Ablatherm® Integrated Imaging HIFU Treatment of Low Risk, Localized Prostate Cancer

P130003

Gastroenterology and Urology Devices Panel Meeting

July 30, 2014

Ablatherm® Robotic HIFU®

Ablatherm® Integrated Imaging HIFU Treatment of Low Risk, Localized Prostate Cancer

P130003

Gastroenterology and Urology Devices Panel Meeting

July 30, 2014

CI-1

Presenters

Cary Robertson, MD

- Associate Professor of Urology, Duke University Medical Center
- Coordinating Principal Investigator of the IDE Study

Inderbir Gill, MD

- Professor and Chair of Urology, University of Southern California
- Medical Monitor of the IDE Study

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Presenters

EDAP-TMS Representatives

Marc Oczachowski

- Chief Executive Officer, EDAP

Emmanuel Blanc

- Chief Technology Officer, EDAP

John Rewcastle, PhD

- Medical Director, EDAP
- Clinical Professor of Urology, University of Southern California

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Agenda

Introduction	Marc Oczachowski
Prostate Cancer in the USA	Inderbir Gill, MD
Device Description	Cary Robertson, MD
Pre Clinical Data	Emmanuel Blanc
Clinical Environment	John Rewcastle, PhD
IDE Trial	John Rewcastle, PhD
Effectiveness Results	Inderbir Gill, MD
Safety Results	Cary Robertson, MD
Body of Evidence Discussion	John Rewcastle, PhD
Post Approval Study	John Rewcastle, PhD
Conclusions	Inderbir Gill, MD

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Introduction

- Opening Remarks
- EDAP TMS Overview
- Prostate Cancer in the USA
- Design Motivation

Presenters

Marc Oczachowski
Inderbir Gill, MD

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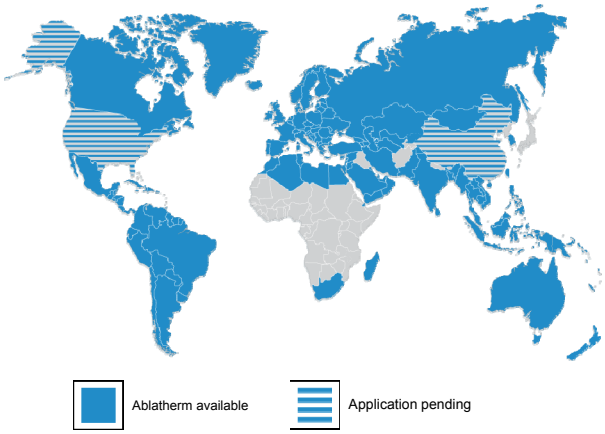
Ablatherm Robotic HIFU - Opening Remarks

260 clinical sites - **40,000** treatments



- Non Invasive Technology that ablates prostatic tissue
- Fully Robotic it creates Safe and precise lesions at the targeted area.
- Proven and recommended worldwide as part of the Patient choice.

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Ablatherm HIFU: Indications for Use

- The Ablatherm Integrated Imaging is intended for the primary treatment of prostate cancer in subjects with low risk, localized prostate cancer.

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Prostate Cancer in the United States

- **233,000** diagnosed in 2014 in the USA[1]
  - most commonly diagnosed cancer in men
- **29,480** deaths in 2014 in the USA[1]
  - second deadliest cancer in men
- **~50%** of newly diagnosed prostate cancer is low-risk[1]
  - (PSA < 10 ng/ml; Gleason ≤ 6; stage ≤ T2a)

However, a low risk diagnosis is not definitive:

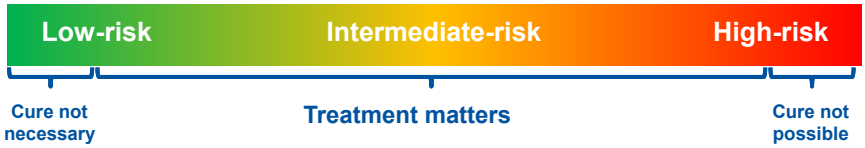
- 34-49% of cases are undergraded[2,3]
- 10-13% of cases are understaged[2,3]

"Low risk" is not necessarily low risk.

1. Cancer Facts and Figures 2014, American Cancer Society; excluding basal and squamous cell skin cancers; 2. Jalloh M et al Eur Urol. 2014 Epub; 3. Busch J et al BJU Int. 2013 Epub;

CI-8

Prostate Cancer in the United States



Primary treatment options include:

- Active surveillance
- Radical prostatectomy (RP)
- Radiation therapy (RT)
- Cryotherapy

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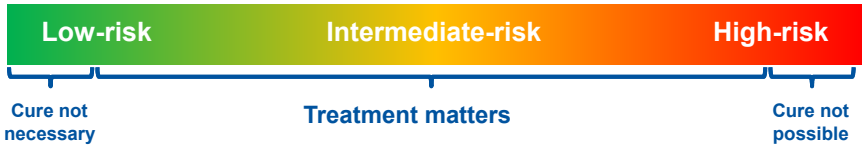
Prostate Cancer in the United States



Primary treatment options include:

- **Active surveillance**
- Radical prostatectomy (RP)
- Radiation therapy (RT)
- Cryotherapy

- 33% discontinue at 3 years[1]
- 3.5% biopsy infection risk/Bx[2]
  - OR increases 1.3 for <u>each</u> previous biopsy

1. Thomsen FB et al J Surg Oncol. 2014 Jun;109(8):830-5; 2. Ehdaie B, et al J Urol. 2014 Mar;191(3):660-4.

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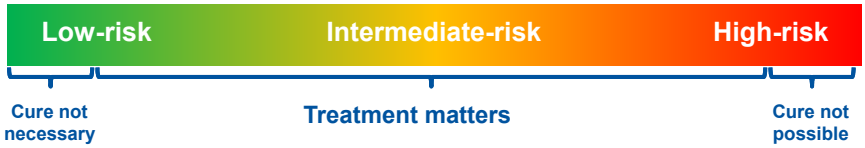
Prostate Cancer in the United States



Primary treatment options include:

- Active surveillance
- **Radical prostatectomy (RP)**
  - Surgical risks
  - Volume dependent outcomes
- Radiation therapy (RT)
- Cryotherapy

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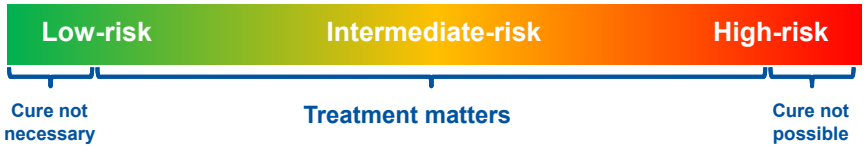
Prostate Cancer in the United States

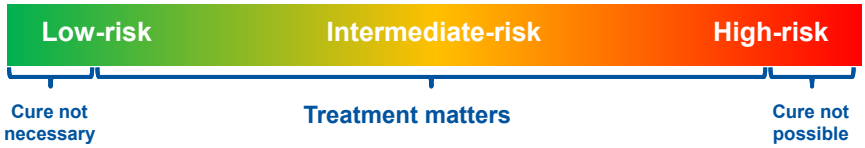


Primary treatment options include:

- Active surveillance
- Radical prostatectomy (RP)
- **Radiation therapy (RT)**
  - Dosing limitations
  - Radiation fears
- Cryotherapy

CI-12

Prostate Cancer in the United States



Primary treatment options include:

- Active surveillance
- Radical prostatectomy (RP)
- Radiation therapy (RT)
- **Cryotherapy**
  - Treatment inaccuracy
  - Near universal ED

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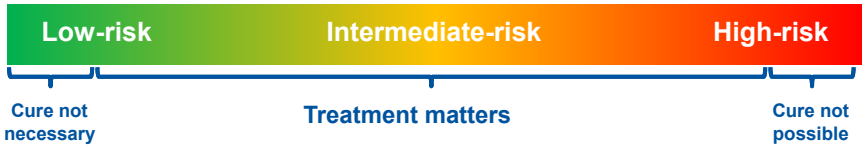
Prostate Cancer in the United States



Primary treatment options include:

- Active surveillance
- Radical prostatectomy (RP)
- Radiation therapy (RT)
- Cryotherapy

No therapeutic approach is perfect and all have limitations

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Ablatherm Integrated Imaging Design Motivation

Ablatherm Integrated Imaging was designed to address the limitations of other treatments, resulting in a device that:

- Incorporates multiple safety features
- Effectively ablates prostate cancer tissue
- Highly precise
- Radiation-free
- Robotically controlled and reproducible
- Non-invasive

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Device Description

- HIFU Principles
- Device Description
- Treatment Procedure
- Safety Features

Presenter

Cary Robertson, MD

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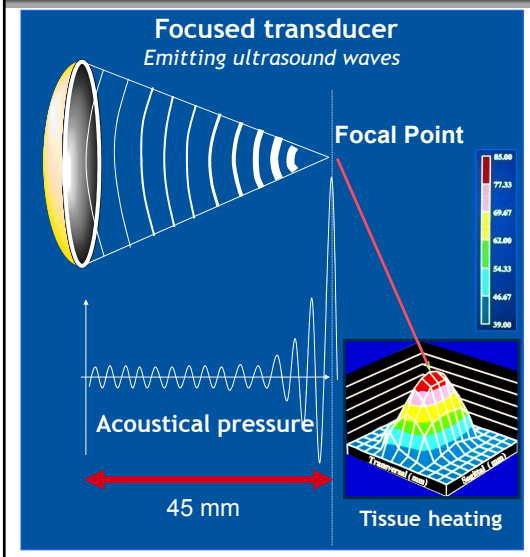
HIFU Principles



Spherical transducer

- Ultrasound waves are emitted by transducer and converge at the transducer focal point.

Acoustical effect

- Pressure wave amplitude dramatically increases in the vicinity of the focal point.

Thermal effect

- Pressure waves create tissue movement, energy absorption and tissue heating concentrated at the focal point.

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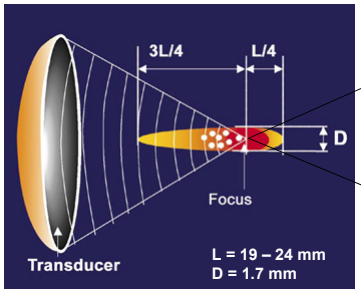
High Intensity Focused Ultrasound (HIFU) Technique



Thermal effect

- Tissue temperature reaches 80°C at the transducer focus within seconds
- Few seconds tissue sonication extends the lesion up to 19 to 24 mm

Mechanical effect

- Generation of gas bubbles
- Collapse of cavities
- Rupture of cell walls

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Treatment Process Video

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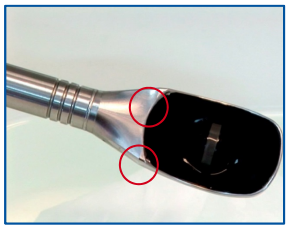
Additional Safety Features

- Device self check when powered ON
- Cycle duration (6s ON, 4s OFF)
- Electrical power measurement (4 samples per cycle)
- Ablapak unique identifier traceability



Thermocouple (on flow outlet)

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Pre Clinical Data

- Precision
- Efficacy
- Safety

Presenter

Emmanuel Blanc

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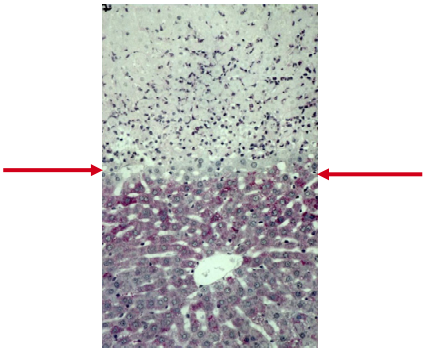
Precise Tissue Effect

- Millimeter accuracy of ablation
- Highly demarcated treatment



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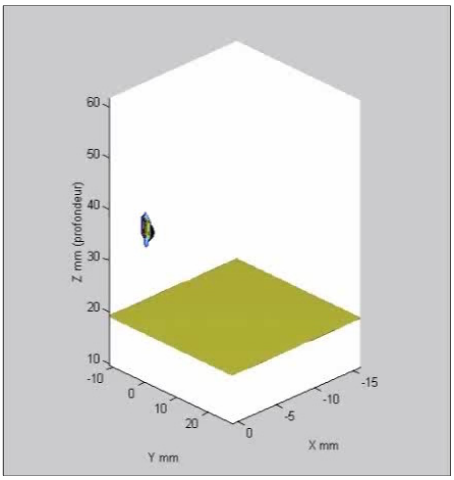
Mathematical Modeling

- Each HIFU lesion deposits energy
- There is a well understood thermal build-up of energy as lesions are created side by side

This effect is optimized to ensure precise homogeneous ablation of the entire prostate



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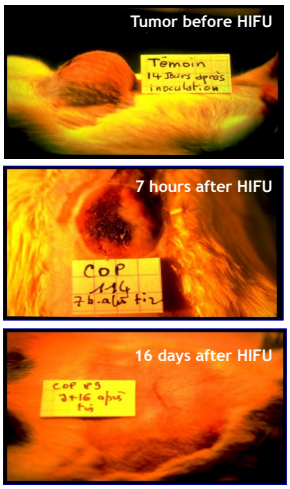
Efficacy

- Treatment efficacy has been evaluated in different tumor models seeded in the abdominal wall of rats
- A similar model has been used to evaluate the risk of HIFU induced metastasis

HIFU ablates cancer cells effectively and does not seed metastasis [1, 2]



1. Chapelon J.Y. et al. Cancer Research 1992, 52: 6353-6357; 2. Oosterhof G.O.N. et al. Eur Urol 1997, 32: 91-95

CI-24

Safety

- A canine model was used to demonstrate the feasibility and safety of an endorectal approach for prostate treatment

- A pilot study including 11 BPH patients was designed to evaluate treatment safety in humans. An adenomectomy was performed 1 week after treatment

HIFU can safely ablate prostate tissue through the rectal wall [1, 2]

1. Gelet A. et al. J. Endourol. 1993, 7, 3: 249-253; 2. Gelet A. Eur Urol 1993, 23 (suppl 1): 44-47

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Clinical Environment

- Regulatory Environment
- Guidelines
- The Ablatherm HIFU Body of Evidence

Presenter

John Rewcastle, PhD

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Regulatory Paths of Prostate Cancer Treatments

Therapy	Technology	Regulatory Path
Surveillance		None
Surgery		None
Laparoscopic	Lap Tools	510(k)
Robotic	Da Vinci	510(k)
Radiation		
XRT/IMRT	Accelerators	510(k)
Brachy	Seeds	510(k)
Cryotherapy	Cryomachines	510(k)
HIFU	Ablatherm	PMA

"Unlike drugs, most devices are cleared for market via the 510(k) process without clinical data."
(J. Baxley, 2013)

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Randomized Clinical Trials in the PSA Era in the USA

Trial	Arm 1	Arm 2	Support	Accrual Target	Final Accrual	% accrued
SWOG 8890	Radical Prostatectomy	External Beam Radiation	NCI	900	6	<1%
SPIRIT	Radical Prostatectomy	Brachytherapy	NCI	1980	56	3%
PIVOT	Radical Prostatectomy	Observation	VA, NCI	2000	731	37%
START	Definitive Treatment	Active Surveillance	NCI	2130	180	9%

Attempts to conduct multi-center RCTs for different localized prostate cancer treatments in the USA have all failed.

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AUA and NCCN Treatment Guidelines

AUA[1]

"Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are appropriate monotherapy treatment options for the patient with low-risk localized prostate cancer."

NCCN[2]

"Observation is recommended for men with low-risk prostate cancer and life expectancy less than 10 years. If the patient's life expectancy is 10 years or more, initial treatment options include: 1) active surveillance; 2) RT or brachytherapy; or 3) radical prostatectomy with or without PLND…"

In absence of RCTs, guidelines are mostly based on cross study comparisons stratified by D'Amico risk group

1. Thompson et al J Urol. 2007 Jun;177(6):2106-31. 2. www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

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The Body of Evidence

We present a diverse body of evidence from multiple investigations of HIFU including:

- **HIFU IDE:**
  - A prospective IDE study in the US and Canada
- **HIFU Registry Cohort and HIFU Long Term Refined Cohort:**
  - Real world data from Europe collected over 15 years
- **HIFU Meta-Analysis (MA):**
  - A systematic review and meta-analysis of the HIFU literature

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The Body of Evidence

Ablatherm HIFU data is compared to several literature sources:

- Cryo MA: a systematic review and meta analysis of the cryotherapy literature used to create a HIFU Performance Goal (PG)
- The radical prostatectomy arm of the Prostate Intervention and Observation Trial (PIVOT RP)
- The radical prostatectomy arm of the Scandinavian Prostate Cancer Group – 4 trial (SPCG-4 RP)

Comparisons are intended to provide perspective and context for the Ablatherm HIFU results.

This diverse body of evidence provides internally consistent evidence of the safety and effectiveness of Ablatherm HIFU

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FDA Regulation (21 CFR 860.7 (c) (2))

*Appropriate data is **valid scientific evidence** from:*

- *Well-controlled investigations,*
- *Partially controlled studies,*
- *Studies and objective trials without matched controls,*
- *Well-documented case histories conducted by qualified experts,*
- *Reports of significant human experience with a marketed device,*

from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

All Ablatherm PMA cohorts meet the definition of *Valid Scientific Evidence*

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IDE Trial

- Original IDE Trial Design
- Accrual Program

Presenter

John Rewcastle, PhD

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Original IDE Study Design

Non-randomized concurrent control of Ablatherm HIFU vs. Cryotherapy

- **Key Inclusion Criteria:**
  - Biopsy proven low risk prostate cancer (PSA<10, Stage ≤T2a; Gleason ≤6)
  - Prostate Volume < 40 cc
  - For HIFU arm only Prostate AP diameter < 25 mm
- **Key Exclusion Criteria**
  - Extraprostatic involvement
  - Previous prostate cancer treatment
  - TURP within the previous year

Accrual target: 384 evaluable subjects

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Original IDE Study Design

- **Primary endpoint:**
  - Achievement of PSA nadir ≤ 0.5 ng/ml and stability of PSA according to ASTRO criteria through 24 months follow up without a positive biopsy.
- **Safety endpoint:**
  - Occurrence of adverse events and device-related adverse events.

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Ablatherm HIFU IDE Study Sites

Ablatherm HIFU IDE Sites	Cryo Sites
Vanderbilt University Medical Center	Cleveland Clinic
Virginia Urology	Triangle Urology (Pittsburgh)
Duke University Medical Center	Chinn and Chinn Urology (LA)
Florida Foundation for Healthcare Research	Scott and White
Urology Associates of Texas	Geisinger Medical Center
University of Colorado	Atlantic Urology (Daytona Beach)
Hackensack University Medical Center	Grand Strand Urology (Myrtle Beach)
Sloan Memorial Kettering Institute	Urology Associates (Fresno)
MD Anderson	Urology Consultants (Pueblo)
Medical College of Wisconsin	Wayne State University
Maple Leaf HIFU	Metro Urology (Minneapolis)
University of North Carolina	University of Calgary
Brooklyn Heights Urology Associates	

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Original IDE Study Design

Accrual was slow, particularly in the control arm, due to:

- Strongly competitive environment from 2005 – 2010 for low-risk PCa:
  - Da Vinci robot adoption (prostatectomy)
  - Intensity Modulated Radiation Therapy (IMRT) adoption
  - Focal cryoablation as an option
  - Active surveillance acceptance for low risk
- Controversy regarding PSA screening
- Prostate size limitation

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IDE Study Design Modifications

EDAP discussed with FDA and agreed to multiple actions to improve accrual including:

- Increased the number of study sites (added 6)
- Added Canadian sites to both arms (Toronto, Calgary)
- Decreased the age limit for inclusion (60 to 50 years)
- Added another cryotherapy device as a control (Galil Medical)
- Increased the anterior-posterior prostate size in the control arm (30mm)

Additionally, EDAP:

- Conducted investigator and coordinator meetings and calls
- Invested in a comprehensive program to increase accrual

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IDE Study Design Modifications

EDAP also discussed with FDA:

- Inclusion of some intermediate risk subjects
- Downsizing of the prostate

Not pursued because of FDA's concerns

FDA held two public meetings to gain insight from a panel of experts on PCa study design:

- December 2009: General Issues Panel Meeting
- May 2013: Prostate Cancer Workshop

Neither panel could provide clear guidance

EDAP made its best efforts to accrue the IDE trial which was impossible due to real-life constraints

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Effectiveness Results

Intermediate Term Effectiveness

- HIFU IDE Study
- HIFU Cohorts

Long Term Effectiveness

- HIFU Long Term Cohort

Context Comparisons

- Cryo Literature
- PIVOT RP
- SPCG-4 RP

Presenter

Inderbir Gill, MD

CI-40

Ablatherm HIFU IDE Study

- IDE data is presented according to the agreed-upon endpoint developed in 2005:
  - achievement of PSA nadir ≤ 0.5 ng/ml and stability of PSA according to ASTRO criteria through 24 months follow up without a positive biopsy.
- A new statistical analysis plan was developed and the current literature standard endpoint for reporting of both Ablatherm HIFU and Cryotherapy outcomes was used to provide context:
  - Phoenix Definition of biochemical failure: PSA nadir + 2.0 ng/ml

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Ablatherm HIFU IDE Study: Demographics

n		135
Age (years)	mean ± SD	64.1 ± 6.7
PSA (ng/ml)	mean ± SD	4.6 ± 2.4
Prostate Vol (cc)	mean ± SD	22.7 ± 12.5
PSA density ng/ml^2		0.2
Gleason Score	6 7(3+4) Not specified	97% 2% 2%
Stage	T1a T1b T1c T2a Not Specified	2% 2% 81% 14% 1%
Race	Caucasian African American Hispanic Multi-Racial Other	82% 13% 3% 1% 1%

Percentage totals may not add to 100% due to rounding

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HIFU IDE: Phoenix Biochemical Success at 2 years

Time Point	Biochemical Success[1]	95% CI
24 Month	90.5%	85.2, 95.8%

1. *Requires at least one PSA obtained at or after 24 months.*

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HIFU IDE: Nadir/ASTRO/Biopsy

Endpoint Components	% (n/N)	95% CI
PSA nadir < 0.5 ng/ml	74% (100/135)	67, 82%
No Positive Biopsy	72% (97/135)	64, 79%
ASTRO Success (no 3 PSA rises)	78% (86/111)	70, 85%

Composite Endpoint	% (n/N)	95% CI
[1]Nadir + ASTRO + negative Bx	50% (61/122)	41, 59%

[1] ASTRO requires minimum of 3 PSA measurements between 6 and 24 months with at least one obtained at or after 24 months. Success determined on absence of positive biopsy, negative biopsy not required.

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HIFU IDE: Biopsy Findings

Positive Biopsy Rate: 28%

Standardized 10 core biopsy: TRUS guided sextant with 4 lateral cores

Biopsy Type	Prostate volume
Diagnostic	35 – 40 cc
HIFU - IDE	8 cc (median)

CI-45

Multi-Modal Treatment Strategies: Low Risk Disease

Radical treatments are often performed with an adjuvant:

- Radical prostatectomy followed by radiation therapy (10-30%)[1,2,3]
- Radiation therapy in combination with androgen deprivation (~50%)[4]
- Cryotherapy in combination with androgen deprivation therapy (~50%)[5]

Jones et al RCT NEJM 2011[6]	Risk Group	n	Bx+
RT	Low	351	35%
RT +ADT	Low	334	12%

No adjuvants in the HIFU IDE

1. http://www.auanet.org/education/guidelines/radiation-after-prostatectomy.cfm, 2. Boorjian et al J Urol. 2008 Apr;179(4):1354-60; 3. Chalfin et al BJU Int. 2012110(11):1684-9; 4. Jones et al N Engl J Med 2011;365:107-18; 5. Jones et al 2008; 180, 554-558 ; 6. Jones et al N Engl J Med 2011;365:107-18.

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HIFU IDE Biopsy Findings: Placing it in Context

	Risk Group	Positive Biopsy rate
AS[1]	Low	~ 80%
RP[2,3]	Low	10-23%
XRT[4,5]	Low	12-35%
Brachy[6,7]	Low	12-15%
Cryo[8]	Not Stratified	4-35%
HIFU[9]	Low	27%
HIFU-IDE	Low	28%

1. Wilt et al N Engl J Med. 2012 Jul 19;367(3):203-13 2. Boorjian et al J Urol. 2008 Apr;179(4):1354-60 3. Chalfin et al BJU Int. 2012 Dec;110(11):1684-9; 4. Jones et al N Engl J Med 2011;365:107-18; 5. Zelefsky et al J Urol. 2008 Apr;179(4):1368-73; 6. Stone et al J Radiat Oncol Biol Phys. 2010 Feb 1;76(2):355-60; 7. Ragde et al Cancer. 1998 Sep 1;83(5):989-1001; 8. Ellis et al Urology. 2007 Feb;69(2):306-10; 9. Jones et al J Urol. 2008 Aug;180(2):554-8.8. Crouzet S. Eur Urol. 2014 May;65(5):907-14.

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HIFU IDE Biopsy Findings: Placing it in Context

	Risk Group	Positive Biopsy rate	10 Year Mets-Free Survival	10 Year Ca-Specific Survival
AS[1]	Low	~ 80%	96%	98%
RP[2,3]	Low	10-23%	99%	100%
XRT[4,5]	Low	12-35%	92-94%	92-94%
Brachy[6,7]	Low	12-15%	96%	88-99% (7 yr)
Cryo[8]	Not Stratified	4-35%	Not available	Not available
HIFU[9]	Low	27%	99%	99%
HIFU-IDE	Low	28%	-	-

1. Wilt et al N Engl J Med. 2012 Jul 19;367(3):203-13 2. Boorjian et al J Urol. 2008 Apr;179(4):1354-60 3. Chalfin et al BJU Int. 2012 Dec;110(11):1684-9; 4. Jones et al N Engl J Med 2011;365:107-18; 5. Zelefsky et al J Urol. 2008 Apr;179(4):1368-73; 6. Stone et al J Radiat Oncol Biol Phys. 2010 Feb 1;76(2):355-60; 7. Ragde et al Cancer. 1998 Sep 1;83(5):989-1001; 8. Ellis et al Urology. 2007 Feb;69(2):306-10; 9. Jones et al J Urol. 2008 Aug;180(2):554-8.8. Crouzet S. Eur Urol. 2014 May;65(5):907-14.

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HIFU Cohorts

- HIFU Meta-Analysis
- HIFU Registry

Presenter

Inderbir Gill, MD

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HIFU MA: Cohort

HIFU MA is a systematic review and Meta-Analysis of HIFU studies.

Searches were performed in PUBMED and EMBASE

- PRISMA methodology followed
- Prospective or retrospective studies included
- Must report safety or low-risk biochemical data
- Whole gland treatment
- Random-effects linear regression models were used

570 articles screened, 13 selected representing 1,193 subjects

CI-50

HIFU Registry Cohort

Line-item data from the Ablatherm HIFU Registry were collected based on the following criteria:

- Low-risk prostate cancer patients
- Pre-treatment prostate volume ≤40 cc at the time of HIFU
- Pre-treatment AP diameter ≤25 mm at the time of HIFU

The Statistical Analysis Plan was defined prior to obtaining the registry data.

115 patients were included in the analysis

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Summary of Intermediate Term HIFU Results

HIFU IDE

Time Point	Biochemical Success	95% CI
2 years	90.5%	85.2, 95.8%

HIFU MA

Time Point	Pooled %	Range
2 Years	92%	74% - 98%
5 Years	83%	66% - 88%

HIFU Registry

Time Point	Biochemical Success	95% CI
2 Years	94.4%	90.0, 98.8%
5 Years	82.9%	74.4, 91.4%

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Cryo Cohorts

- Cryo Retro
- Cryo MA
- HIFU PG based on Cryo MA

Presenter

Inderbir Gill, MD

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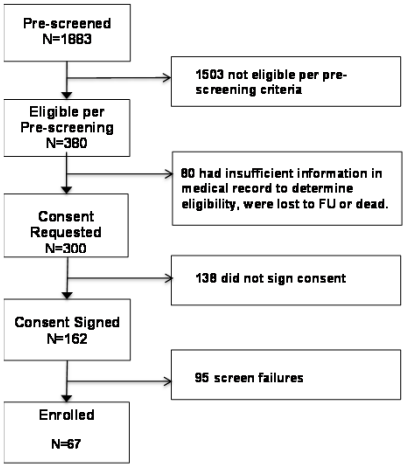
Cryo Retro Cohort



Factors impacting enrollment:

- Strict inclusion criteria

Near universal adjuvant therapy at most centers

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Cryo MA: Systematic Review and Meta-Analysis

Cryo MA is a systematic review and Meta-Analysis of cryotherapy studies

Cryo MA follows the same methodology as HIFU MA

Only included reports of whole-gland cryotherapy

192 articles were screened, 25 selected representing 1,864 subjects

CI-55

Cryo MA: Biochemical Survival

Time Point	Pooled %	Range	n publications
2 Years	87%	69% - 96%	10
5 Years	81%	49% - 93%	7

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Intermediate-Term Effectiveness

Principal Effectiveness Comparison:

- HIFU IDE vs. HIFU PG at 2 years

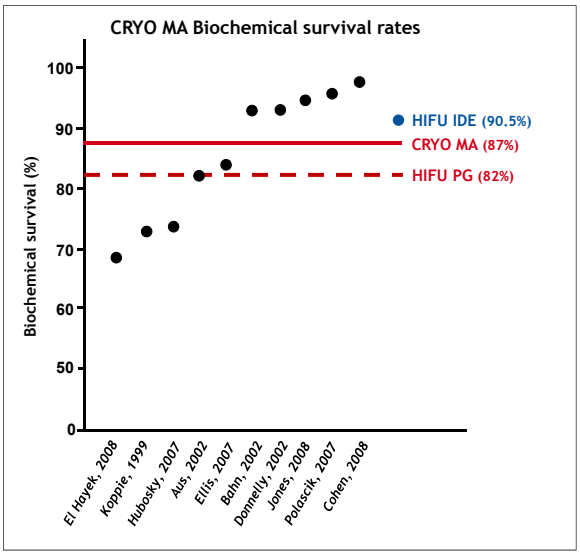
Supporting Comparisons:

- HIFU MA vs. Cryo MA at 2 and 5 years
- HIFU Registry vs. Cryo MA at 2 and 5 years

Three comparisons are presented to provide context of the Biochemical Survival results of Ablatherm HIFU

CI-57

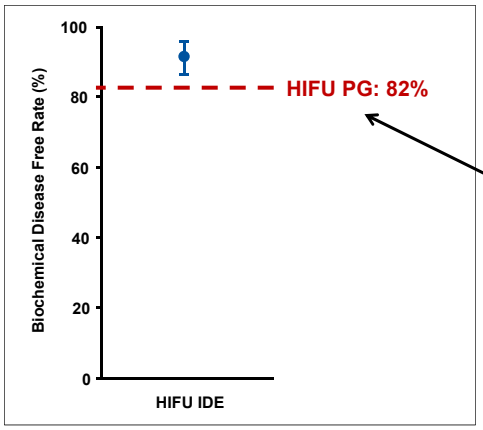
CRYO MA Publications



CI-58
EF-26

Intermediate Term Results: Principal Effectiveness (1)

HIFU IDE vs. Performance Goal at 2 Years



HIFU IDE: 91% (95%CI: 85%, 96%)

Performance Criteria based on meta-analysis of the cryotherapy literature

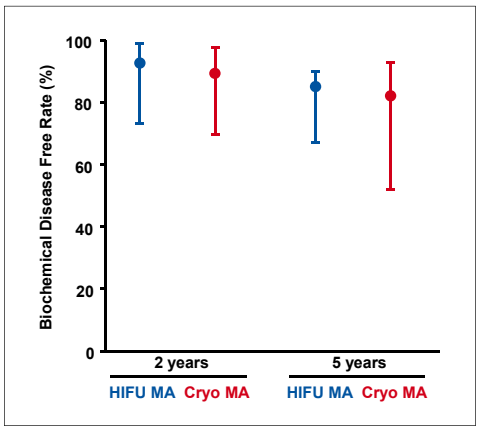
Performance Goal Met: p<0.01

Error bars represent 95% confidence interval

CI-59

Intermediate Term Results: Supporting Effectiveness (2)

HIFU MA vs. Cryo MA at 2 and 5 Years



Internally consistent evidence of comparability at 2 years.

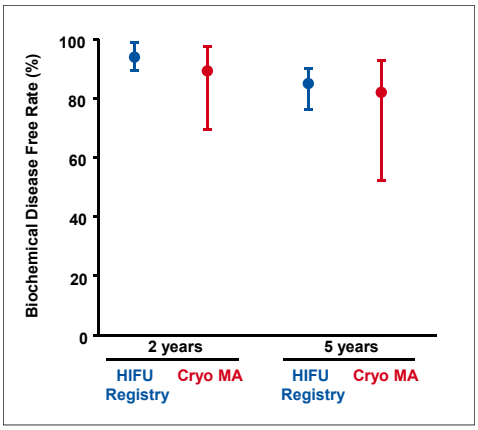
Evidence of comparability at 5 years to cryotherapy effectiveness

Error bars represent range

CI-60

Intermediate Term Results: Supporting Effectiveness (3)

HIFU Registry vs. Cryo MA at 2 and 5 Years



Internally consistent evidence of comparability at 2 years.

Internally consistent evidence of comparability at 5 years to cryotherapy effectiveness

Error bars represent 95% confidence interval for HIFU Registry and range for Cryo MA

CI-61

Intermediate Term Results: Summary of Effectiveness Comparison

The principal effectiveness comparison was met ($p<0.01$)

The supporting comparisons demonstrate internally consistent evidence of comparability at 2 and 5 years.

CI-62

Long Term Effectiveness

- HIFU Long Term Refined Cohort
- Context Comparisons
  - PIVOT RP
  - SPCG-4 RP

Presenter

Inderbir Gill, MD

CI-63

HIFU Long Term Project

- The project was a response to FDA's request to demonstrate safety and non-surrogate effectiveness from a single data set.

	Risk Group	n	10 Year Cancer Specific Survival	10 Year Metastases-Free Survival
Ganzer (Germany)	Low	229	100%	99.6%
	Moderate	211	96.2%	94.3%
Thuroff (Germany)	All localized (72% mod or high)	704	99%	95%
Crouzet (France)	Low	357	99%	99%
	Moderate	452	98%	95%
	High	174	92%	86%

- The data used were derived from databases maintained at three European sites that recently published long-term treatment results of Ablatherm HIFU.

Ganzer R, BJU Int. 2013 Aug;112(3):322-9; Thüroff S, Chaussy C: J Urol. 2013 Aug;190(2):702-10; Crouzet S. Eur Urol. 2014 May;65(5):907-14.

CI-64

HIFU Long Term Project

- Cancer-Specific and Metastasis-free Survivals are standard long-term endpoints for Prostate Cancer

		Risk Group	n	10 Year Cancer Spec Sur	10 Year Mets Free Sur
Boorjian 2008 RP	Mayo Clinic	Low	3283	100%	99%
		Intermediate	2795	97%	94%
		High	1513	95%	89%
Stephenson 2008 RP	MSK CCF U Mich	Low	5200	99%	-
		Intermediate	4184	96%	-
		High	1962	92%	-

Boorjian et al J Urol. 2008 Apr;179(4):1354-60; Stephenson et al J Clin Oncol. 2009 Sep 10;27(26):4300-5

CI-65

HIFU Long Term Project

- Long term large volume state-of-the-art RP studies can be used as a reference

	10 Year Cancer Specific Survival		10 Year Metastasis-Free Survival	
	Prostatectomy	Ablatherm HIFU	Prostatectomy	Ablatherm HIFU
Low	99-100%	99-100%	99%	99-100%
Intermediate	96-97%	96-98%	94%	94-95%
High	92-95%	92%	89%	86%

Ganzer R, BJU Int. 2013 Aug;112(3):322-9; Thüroff S, Chaussy C: J Urol. 2013 Aug;190(2):702-10; Crouzet S. Eur Urol. 2014 May;65(5):907-14. Boorjian et al J Urol. 2008 Apr;179(4):1354-60; Stephenson et al J Clin Oncol. 2009 Sep 10;27(26):4300-5

CI-66

HIFU Long Term Refined Cohort

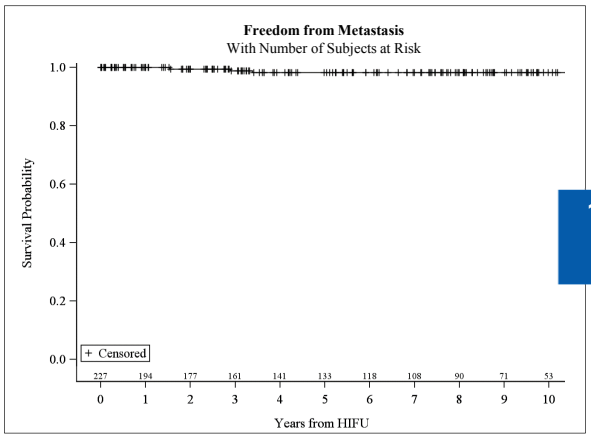
The HIFU Long Term Refined Cohort is a prospectively defined retrospective data collection from the 3 European centers:

- Line-item data
- Low-risk prostate cancer patients
- Prostate volume ≤40 cc at HIFU
- AP diameter ≤25 mm at HIFU
- No previous TURP or Hormones

227 patients were included in the analysis

CI-67

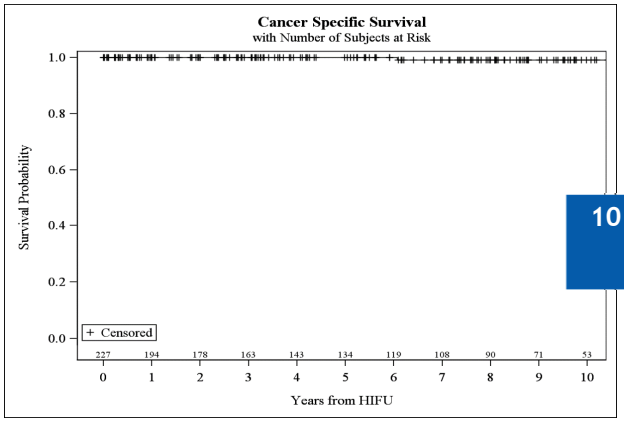
HIFU Long Term Refined Cohort: Freedom from Metastasis



10 Year Freedom From Metastasis: 98.2%
(95% CI: 94.5%, 99.4%)

CI-68

HIFU Long Term Refined Cohort: Prostate Cancer Specific Survival

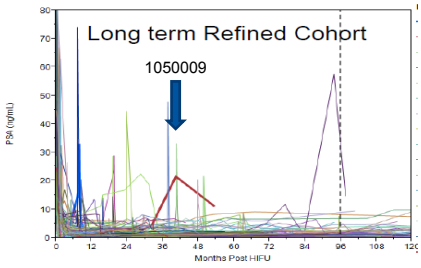


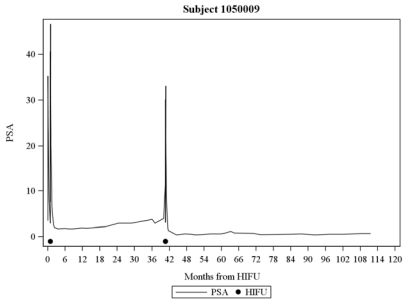
10 Year Cancer Specific Survival: 99.1%
(95% CI: 94.2%, 99.9%)

CI-69

PSA Spike after HIFU

- In the perioperative period approximately 50% of HIFU patients exhibit a PSA spike following the ablation of tissue [1]
- This is an expected effect and not correlated with subsequent biochemical failure[1]
- Care needs to be taken when interpreting individual or superimposed PSA histories if they include repeat HIFU.





Inamoto et al Clin Med Insights Oncol. 2011; 5: 101-106.

CI-70

PIVOT

Prostate Cancer Versus Intervention Trial (PIVOT)[1]

- Veterans Affairs population
  - High co-morbidities, lower life expectancy
  - Not similar to the general population
- Conducted between 1994 and 2002; published in 2012
- Only 731 of 2000 patients were accrued (148 low-risk RP)
- Not all subjects underwent assigned treatment
- An apparent benefit was observed but not statistically established
- The trial was not designed to show a benefit in sub groups

The statistical limitations of PIVOT's comparison of Observation to RP are not relevant to our comparison to RP to provide context.

1. Wilt et al. N Engl J Med. 2012 Jul 19;367(3):203-13; 2. Bill-Axelson et al N Engl J Med. 2011 May 5;364(18):1708-17

CI-71

SPCG-4

Scandinavian Prostate Cancer Group-4 Trial (SPCG-4) [2]

- Conducted between 1989 and 1999 in Scandinavia; published in 2011
- 695 men randomly assigned to observation or radical prostatectomy
- 166 low risk subjects in the RP arm

1. Wilt et al. N Engl J Med. 2012 Jul 19;367(3):203-13; 2. Bill-Axelson et al N Engl J Med. 2011 May 5;364(18):1708-17

CI-72

Long Term Effectiveness

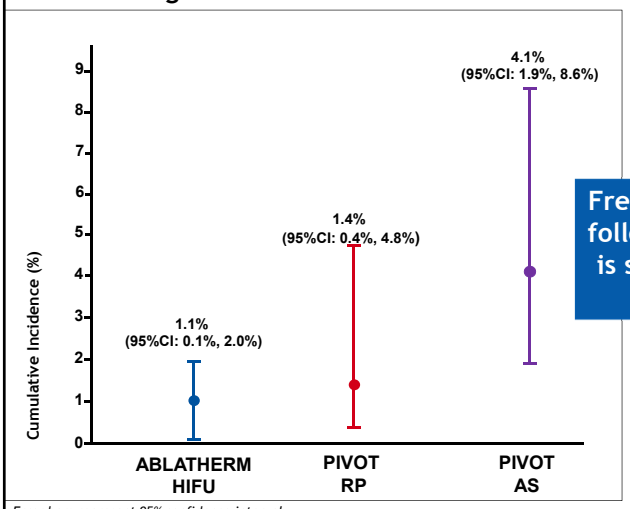
Four comparisons are presented to provide context of the of long term effectiveness of Ablatherm HIFU

CI-73

Principal Effectiveness: Metastasis at 8 Years

(1)

HIFU Long Term Refined Cohort vs. PIVOT



Error bars represent 95% confidence interval

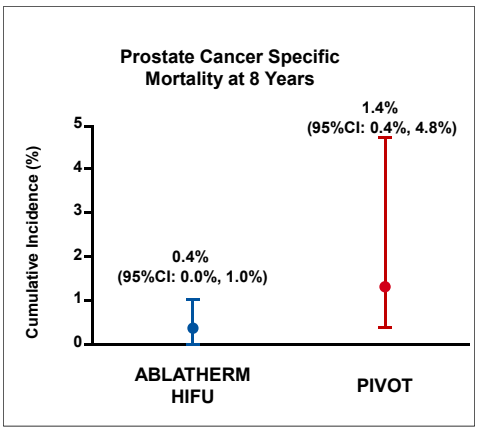
Freedom from metastasis following Ablatherm HIFU is similar to PIVOT RP at 8 years

CI-74

Supporting Effectiveness: PCa Mortality at 8 Years

HIFU Long Term Refined Cohort vs. PIVOT RP

(2)



Prostate Cancer Specific Survival following Ablatherm HIFU is similar to PIVOT RP

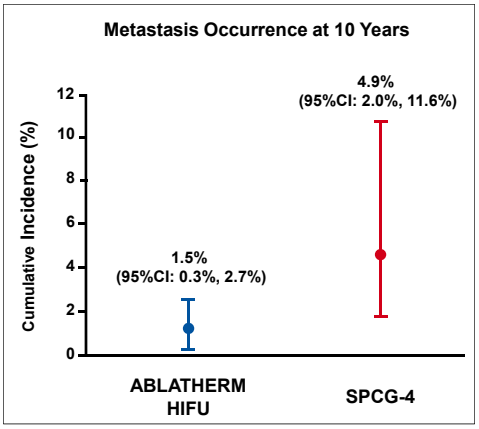
Error bars represent 95% confidence interval

CI-75

Supporting Effectiveness: Metastasis at 10 Years

HIFU Long Term Refined Cohort vs. SPCG-4 RP

(3)



Freedom from metastasis following Ablatherm HIFU is similar to SPCG-4 RP

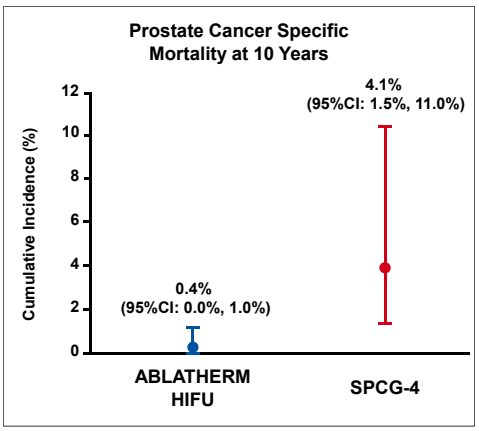
Error bars represent 95% confidence interval

CI-76

Supporting Effectiveness: PCa Mortality at 10 Years

HIFU Long Term Refined Cohort vs. SPCG-4 RP

(4)



Prostate Cancer Specific Survival following Ablatherm HIFU is similar to SPCG-4 RP

Error bars represent 95% confidence interval

CI-77

Long Term Results: Summary of Effectiveness Comparison

The principal comparison demonstrated similar effectiveness

Three supporting comparisons consistently demonstrated similarity of Ablatherm HIFU results to PIVOT and SPCG-4 Radical Prostatectomy

CI-78

Safety Results

- Ablatherm HIFU IDE Safety Results
- Ablatherm HIFU Safety Context
  - HIFU MA vs Cryo MA
  - HIFU IDE and HIFU Safety Cohort vs PIVOT RP

Presenter

Cary Robertson, MD

CI-79

Ablatherm HIFU IDE Safety Findings

	All AEs
Adverse event	Occurrence
Any	97%
Moderate/Severe	82%
Severe	41%
ED	67%
Ur. Incontinence	39%
Stricture[1]	35%
Ur. Retention[2]	49%
Bowel injury[3]	4%
Urethral injury[4]	15%
Bowel dys'n[5]	21%

Rigorous follow-up captured all AEs in the HIFU IDE Cohort

This comprehensive level of AE reporting is typically not reflected in the literature.

[1] Bladder neck contracture, narrowing of prostatic urethra, prostate obstruction, meatal stenosis, urinary stricture
[2] Obstruction, urinary restriction, urinary obstruction, urinary retention, bladder outlet obstruction, unable to empty bladder [3] Anal tears, ischemic bowel injury with fistula [4] Urethral perforation, urethral sloughing, tissue flap, submucosal hematomas [5] Constipation, diarrhea, hemorrhoidal pain, nausea, ischemic bowel, vomiting, rectal bleed, unrelated GI, irritated bowel movement

CI-80

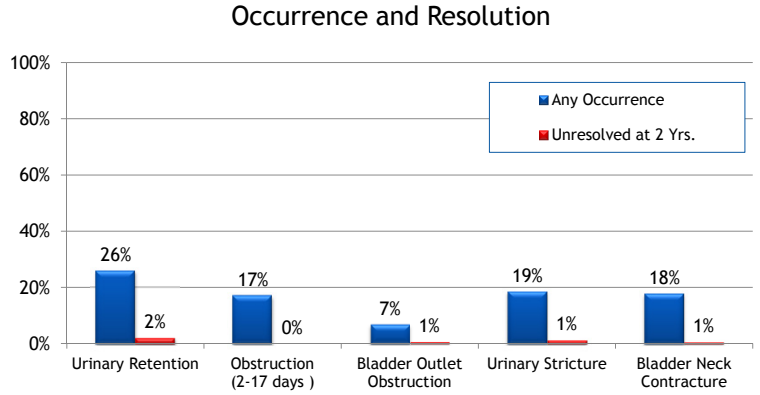
Ablatherm HIFU IDE Safety Findings

	All AEs	Moderate or Severe AEs Related to Device or Procedure	
Adverse event	Occurrence	Occurrence	Unresolved
Any	97%	80%	47%
Moderate/Severe	82%	80%	47%
Severe	41%	34%	12%
ED	67%	52%	38%
Ur. Incontinence	39%	10%	3%
Stricture[1]	35%	27%	1%
Ur. Retention[2]	49%	41%	3%
Bowel injury[3]	4%	0%	0%
Urethral injury[4]	15%	4%	0%
Bowel dys'n[5]	21%	7%	1%

[1] Bladder neck contracture, narrowing of prostatic urethra, prostate obstruction, meatal stenosis, urinary stricture
[2] Obstruction, urinary restriction, urinary obstruction, urinary retention, bladder outlet obstruction, unable to empty bladder [3] Anal tears, ischemic bowel injury with fistula [4] Urethral perforation, urethral sloughing, tissue flap, submucosal hematomas [5] Constipation, diarrhea, hemorrhoidal pain, nausea, ischemic bowel, vomiting, rectal bleed, unrelated GI, irritated bowel movement

CI-81

HIFU IDE: Urinary Obstructive Morbidity

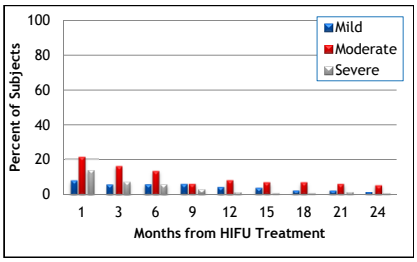


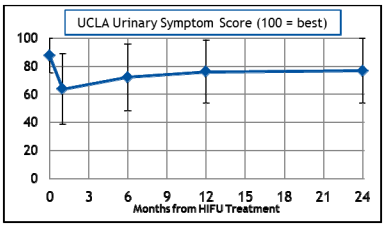
Urinary Obstructive symptoms, likely related to the ablation of the prostatic urethra are common, but most often resolve

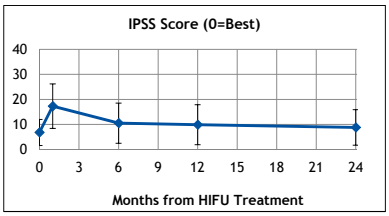
CI-82

HIFU IDE: Urinary Obstructive Morbidity

HIFU IDE Urinary Adverse Events by Follow-up Time





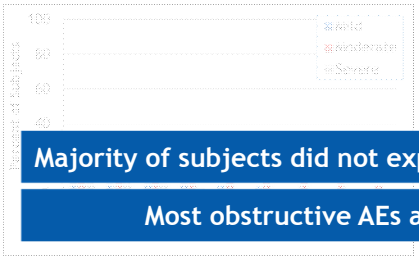


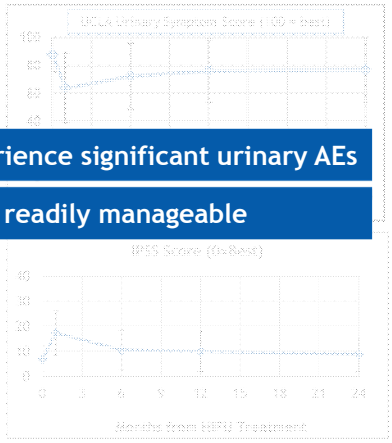
Urinary adverse events largely resolve in 6-12 months

CI-83

HIFU IDE: Urinary Obstructive Morbidity

HIFU IDE Urinary Adverse Events by Follow-up Time





Majority of subjects did not experience significant urinary AEs

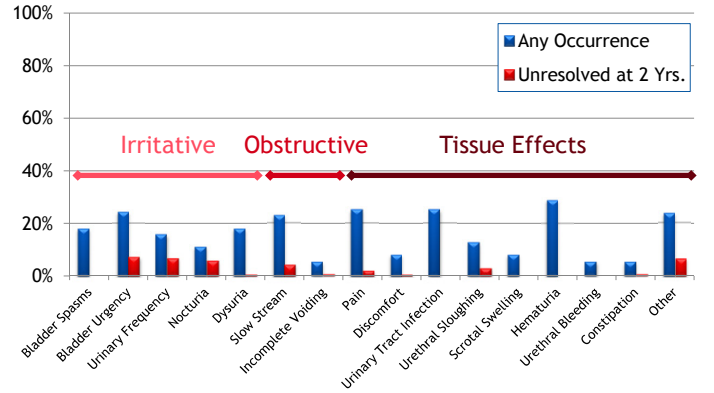
Most obstructive AEs are readily manageable

Urinary adverse events largely resolve in 6-12 months

CI-84

HIFU IDE: Other Morbidity

Occurrence and Resolution

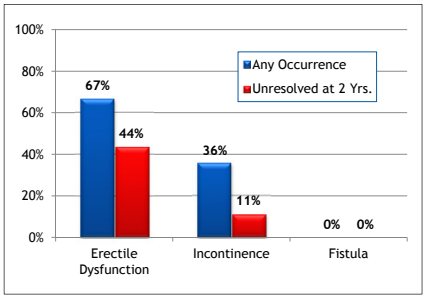


Other AEs which are common with any prostate cancer therapy and tend to resolve with time

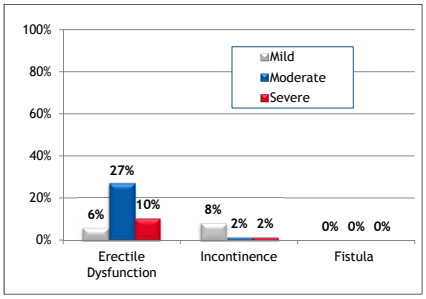
CI-85

HIFU IDE: ED, Incontinence and Fistula

Occurrence and Resolution



Severity of Unresolved



ED, incontinence and fistula are the most clinically important prostate treatment AEs
Some ED persists, most incontinence resolves and fistulae have not been observed

CI-86

HIFU Prospective Safety Cohort: Demographics

n		62
Age (years)	mean ± SD (n)	70.3 ± 5.6
PSA (ng/ml)	mean ± SD (n)	5.9 ± 2.3
Prostate Vol at treatment (cc)	mean ± SD (n)	26.1 ± 7.0
Gleason Score	2 3 4 5 6	- - 3% 15% 82%
Stage	T1a T1b T1c T2a	2% 3% 61% 34%

CI-87

HIFU Prospective Safety Cohort: Results

Adverse Events	Observed in
Any	63%
Erectile Dysfunction	29%
Urinary Incontinence	27%
Urinary Retention resolved by day 30	10%
Urinary Retention not resolved by day 30 or onset ≥ 30 days	2%
Anal Tears	2%
Bleeding requiring transfusion	0
Urinary Tract Infection	19%

CI-88

HIFU MA: Adverse Events

HIFU MA	Median	IQR	n publications
ED	43 %	36.3, 50.0	9
Incontinence	9 %	6.2, 15.6	12
Retention	14 %	7.4 - 19.3	4
Obstruction	17 %	12.9, 20.2	4
Stricture	11 %	7.3, 14.7	6
Fistula	0 %	0.0, 0.6	3

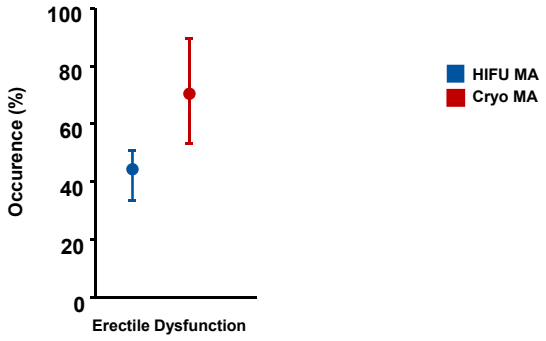
CI-89

Cryo MA: Adverse Events

Cryo MA	Median	IQR	n publications
ED	70 %	53.0, 89.8	17
Incontinence	8 %	3.9, 17.2	23
Retention	4 %	2.2, 9.5	12
Obstruction	15 %	11.9, 21.8	3
Stricture	0 %	0.0, 5.2	5
Fistula	0 %	0.0, 0.5	15

CI-90

Principal Safety Comparison: HIFU MA vs. Cryo MA – Erectile Dysfunction

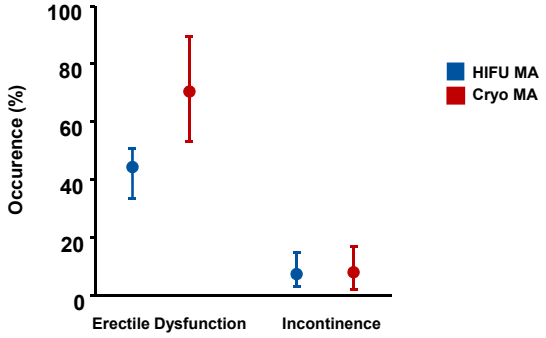


Erectile Dysfunction is lower following HIFU than cryo

Box represents IQR; error bars represent range

CI-91

Principal Safety Comparison: HIFU MA vs. Cryo MA – Incontinence

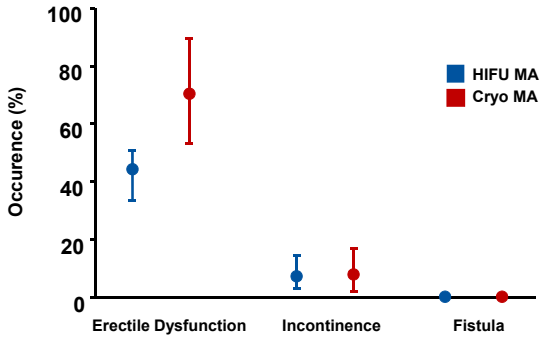


Erectile Dysfunction is lower following HIFU than cryo
Incontinence is similar

Box represents IQR; error bars represent range

CI-92

Principal Safety Comparison: HIFU MA vs. Cryo MA – Fistula

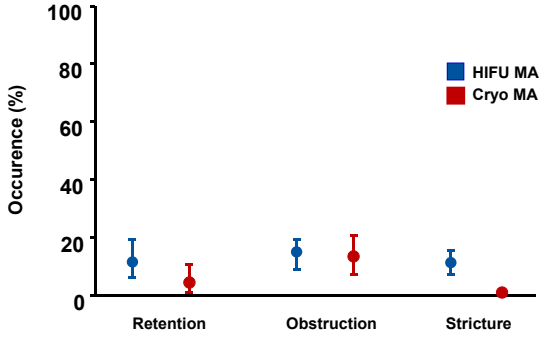


Erectile Dysfunction is lower following HIFU than cryo
Incontinence is similar
Fistulae are rare

Box represents IQR; error bars represent range

CI-93

Principal Safety Comparison: HIFU MA vs. Cryo MA – Urinary morbidity



Retention and stricture are higher following HIFU.
Obstruction is similar

Box represents IQR; error bars represent range

CI-94

Principal Safety Comparison: HIFU MA vs. Cryo MA

Urinary obstructive symptoms are more common following HIFU than Cryotherapy

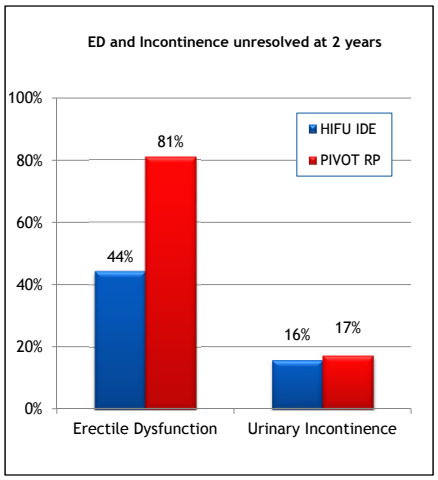
These are most often temporary

ED is more common following Cryotherapy

This is most often permanent

CI-95

Ablatherm HIFU Adverse Events vs. RP Erectile Dysfunction and Incontinence



At 2 years:

- ED is less frequent following Ablatherm HIFU than PIVOT RP
- Incontinence is similar to PIVOT RP

CI-96

Ablatherm HIFU Adverse Events vs. RP Obstructive Urinary Morbidity

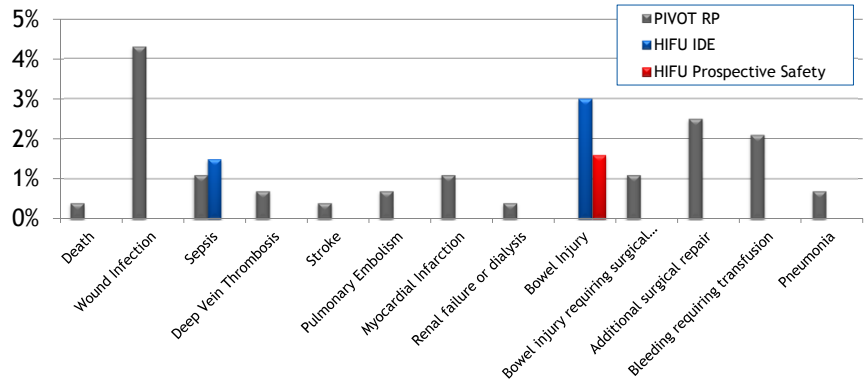
Adverse Events	HIFU IDE	PIVOT RP
Urinary Obstruction	24%	Not Reported
Urinary Stricture	19%	Not Reported
Bladder Neck Contracture	18%	Not Reported
Perioperative Urinary Retention Resolved by day 30 Not resolved by 30 days	 9% 9%	 Not Reported 2%
Retention onset > 30 days	13%	Not Reported

Urinary Obstructive AEs were not reported in PIVOT RP

In the HIFU IDE obstructive AEs are observed but are likely related to the ablation of the prostatic urethra and most often resolve

CI-97

Ablatherm HIFU Adverse Events vs. RP Other Morbidity



Although infrequent, severe AEs occur after Radical Prostatectomy

They are not associated with HIFU

**Sepsis in the IDE was not related to the Ablatherm HIFU device or procedure; bowel injuries were anal tears*

CI-98

Safety Comparison Comments:

Ablatherm HIFU compared to PIVOT RP had less ED and similar incontinence.

Ablatherm HIFU had higher obstructive symptoms, which generally resolved.

RP had infrequent but severe AEs.
Ablatherm HIFU did not.

CI-99

Limitations

Presenter

John Rewcastle, PhD

CI-100

Limitation 1: Choice of Endpoints

No consensus on endpoints

- Intermediate-term standard: Biochemical Survival
- Long-term: Freedom from metastasis and Cancer-specific Survival
- EDAP evaluated all these endpoints

CI-101

Limitation 2: Comparison

Cross-study comparisons are challenging

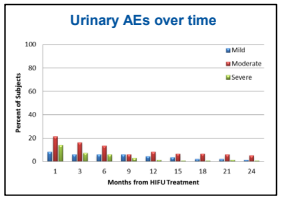
- Each comparison provides context
- They demonstrate internal consistency
- In totality they are compelling

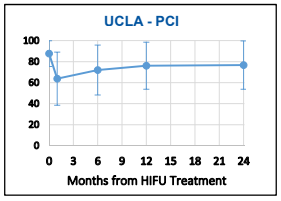
CI-102

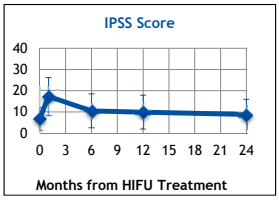
Limitation 3: Urinary Morbidity Interpretation

Perioperative urinary morbidity after HIFU occurs

- Occurs up-front and resolves quickly
- Expected part of the healing process
- Urinary Quality of Life returns







CI-103

Post Approval Study

- Design
- Endpoints

Presenter

John Rewcastle, PhD

CI-104

Post Approval Study Design

On Label (primary whole gland HIFU)
Uncontrolled (single arm), n = 500
Multi center (up to 15 investigational sites)

Key Inclusion Criteria:

- Male subject, age > 50 years
- Biopsy proven low risk prostate cancer (PSA<10, Stage ≤T2a; Gleason ≤6)

Key Exclusion Criteria:

- Evidence of seminal vesicle involvement, lymph node involvement or metastasis
- Any previous treatment for prostate cancer; including EBRT, hormone therapy and/or previous bilateral orchiectomy

CI-105

Post Approval Study Design

Primary Endpoint:

- The occurrence of prostate cancer metastasis 8 years post Ablatherm HIFU

Secondary endpoints:

- Overall survival following Ablatherm HIFU
- Cancer specific survival following Ablatherm HIFU
- Freedom from salvage treatment following Ablatherm HIFU
- Adverse events and device- and procedure-related adverse events
- Morbidity at 2 years

CI-106

Conclusions

- Safety
- Effectiveness
- Risk-benefit

Presenter

Inderbir Gill, MD

CI-107

Safety Summary: Device Design

- **Procedure Safety** → Multiple technical safety features
- **Reliability** → Robotic control
- **Accuracy** → Highly precise
- **Reproducibility** → Non operator-dependent ablation

CI-108

Safety Summary: Clinical Findings

- Erectile Dysfunction → Less frequent than Cryo and PIVOT RP
- Urinary obstructive morbidity → Transient in most cases
- Incontinence → Similar to Cryo and PIVOT RP
- Severe Surgical AEs → None observed following HIFU

CI-109

Effectiveness Summary

- Precise energy delivery → Greater accuracy than Cryo
- Proven ablation → Achieves whole gland treatment
- Positive Biopsy Rate → Similar to other treatments
- 2 to 5 year Biochemical Survival → Similar to Cryo
  - ✓ Demonstrated through several consistent comparisons
- 8 to 10 year Freedom from metastasis and PCa Survival → Similar to PIVOT RP and SPCG-4 RP
  - ✓ Demonstrated through several internally-consistent comparisons

CI-110

Risk-Benefit of Ablatherm HIFU

Risks

- Morbidity profile not dissimilar to other PCa therapies
- Urinary obstructive morbidity higher following HIFU (but transient)

Benefits

- Non Invasive Procedure
- Definitive Local Therapy
- Cancer Control
- Precise Energy Delivery with Automated Safety Features
- More Frequent Preservation of Erectile Function
- Avoidance of infrequent but serious surgical adverse events
- Preservation of Treatment Options

CI-111

Ablatherm Robotic HIFU - Concluding Remarks

Although this is not a traditional PMA application:

- HIFU is a well understood and proven ablation technology
- Pre clinical data supports the clinical use of the device
- Ablatherm Integrated Imaging is a sophisticated technology safely utilized around most of the world today
- Multiple scientifically valid HIFU cohorts, including ten year outcomes, are presented
- Comparisons are made to the best available cryotherapy and prostatectomy cohorts to provide context

The body of evidence provides reasonable assurance of safety and effectiveness and demonstrates the benefits outweigh the risks

CI-112

Thank you

CI-113