

TERAPIA FOCAL EN CÁNCER DE PRÓSTATA: UNA POTENCIAL ESTRATEGIA PARA SOLUCIONAR EL PROBLEMA DEL SOBRETREATAMIENTO

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CÁNCER DE PRÓSTATA LOCALIZADO TERAPIA FOCAL

Tratamiento individualizado que selectivamente realiza la ablación del tejido tumoral conocido con preservación funcional para minimizar la morbilidad sin comprometer la expectativa de vida.

Consiste en una ablación subtotal de la próstata que elimine el cáncer preservando el tejido que lo envuelve para mantener la calidad de vida del paciente conservando su erección, continencia y función intestinal.

La terapia ideal permitiría tratar el lado de la enfermedad sin afectar el paquete neurovascular en el lado contralateral.

CANCER DE PRÓSTATA LOCALIZADO

OPCIONES DE TRATAMIENTO

Vigilancia Activa

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graph TD; A[Vigilancia Activa] --> B[Terapia Focal]; B --> C[Prostatectomía Radical / Radioterapia];
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Terapia Focal

Prostatectomía Radical / Radioterapia

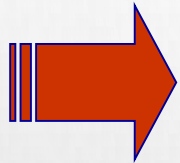
CANCER DE PROSTATA LOCALIZADO CONTROVERSIAS EN LA TERAPIA FOCAL

¿Vigilancia Activa o Terapia Focal?

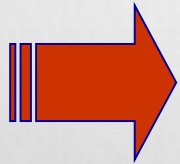
- MAYOR MORBILIDAD CON RESULTADOS ONCOLÓGICOS NO DESCRITOS
- TERAPIA DE RESCATE TRAS FALLO DE LA TERAPIA FOCAL NO CLARO
 - **MANEJO TEMPRANO DE ENFERMEDAD ÓRGANO-CONFINADA**

CANCER DE PROSTATA LOCALIZADO TERAPIA FOCAL

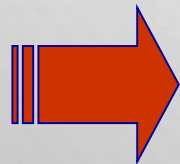
Premisas



Se puede estadificar con precisión el CP y se pueden detectar todos los tumores significativos.



La Terapia Focal debería ser capaz de erradicar de forma total y eficaz todos los focos tumorales.



El tratamiento de los focos tratados debe mejorar la morbilidad y mortalidad específica del CP mejorando los resultados del seguimiento vigilado.

- Eggener SE. and cols. Focal Therapy for localized prostate cancer: a critical appraisal of rationale and modalities, J Urolo 2007, 176(6): 2260-2267.

CANCER DE PRÓSTATA LOCALIZADO

OBJETIVO DE LA TERAPIA FOCAL

"Tratar el cáncer,
no a la próstata"

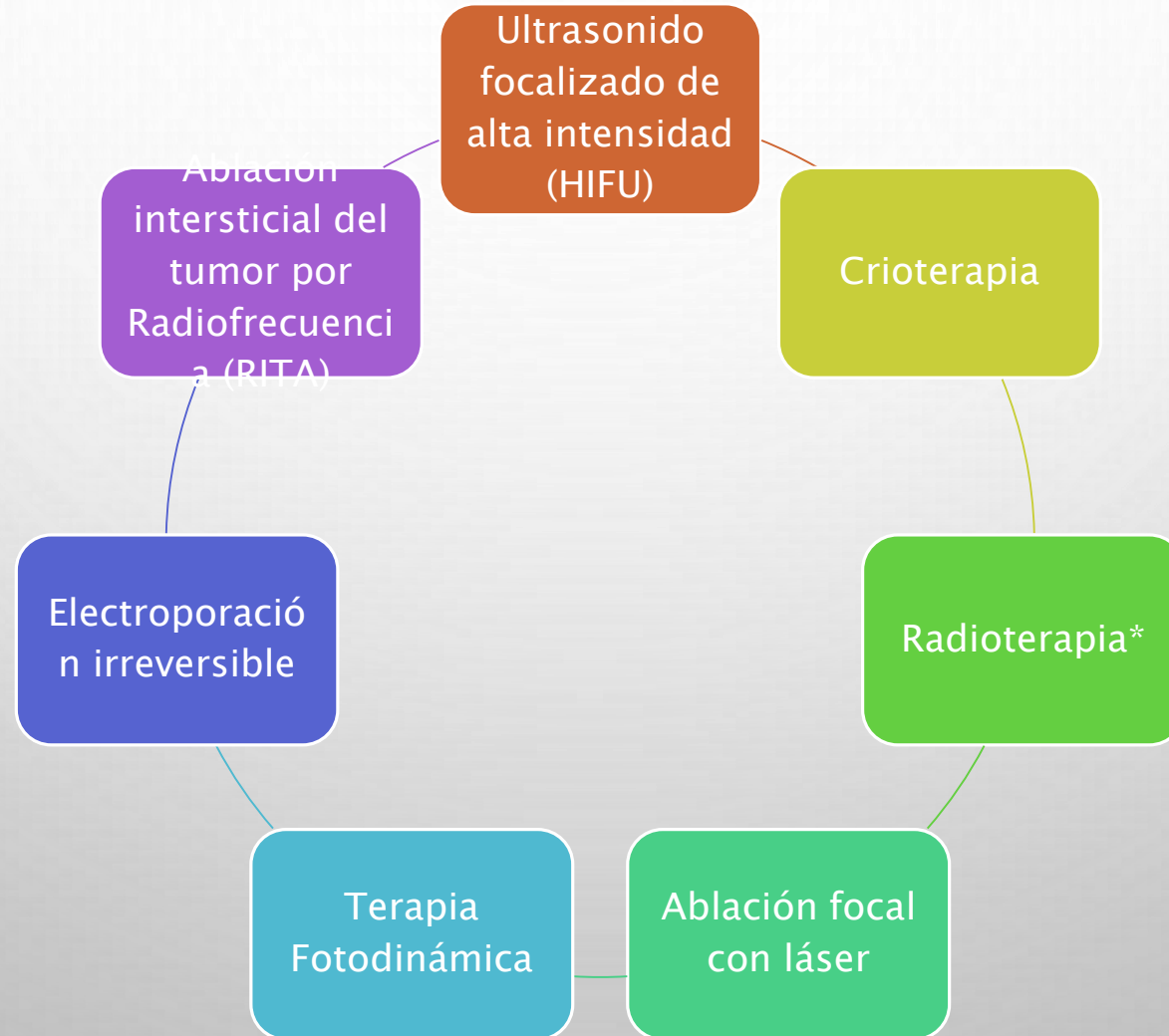
↓ Morbilidad

= Control
oncológico

COMPARACIÓN:
Prostatectomía radical
Radioterapia de haz
externo

CANCER DE PROSTATA LOCALIZADO

MODALIDADES DE TERAPIA FOCAL



CANCER DE PRÓSTATA LOCALIZADO IMAGEN Y BIOPSIA

- EL ÉXITO DE LAS TERAPIAS FOCALES RADICA EN LA IDENTIFICACIÓN PRECISA DE LA LESIÓN (CA. DE PRÓSTATA). DEPENDE DE:

Resonancia Magnética de Próstata
multiparamétrica (RMmp)

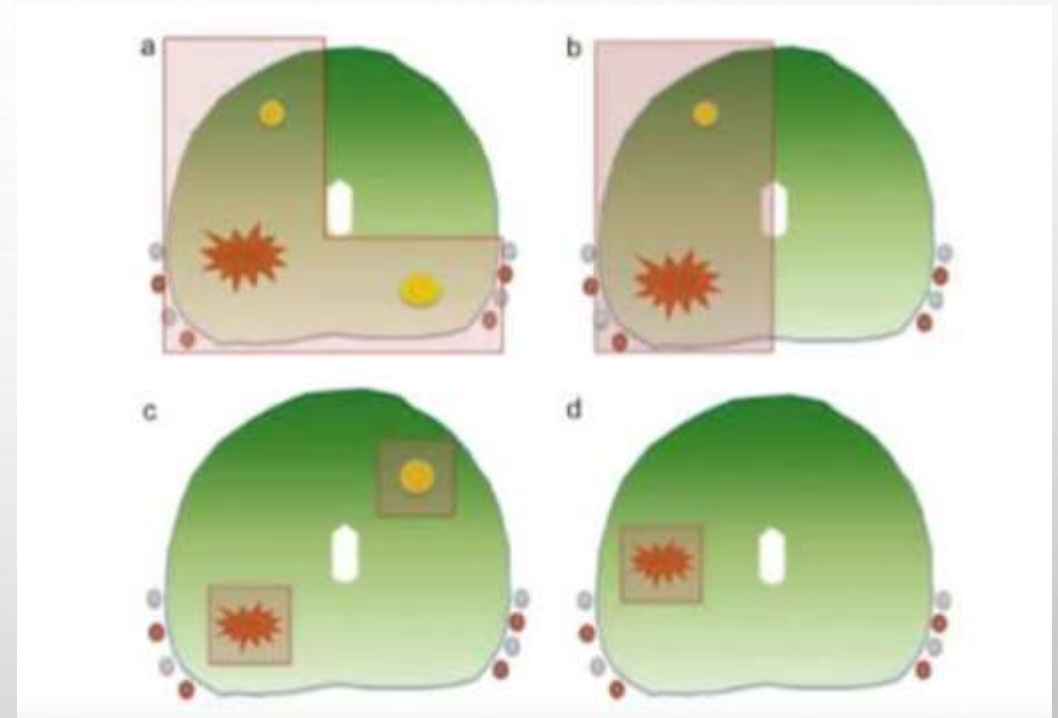
Biopsia – sistemática y dirigida por
fusión

CÁNCER DE PRÓSTATA LOCALIZADO

LOCALIZACIÓN Y LESIÓN A TRATAR

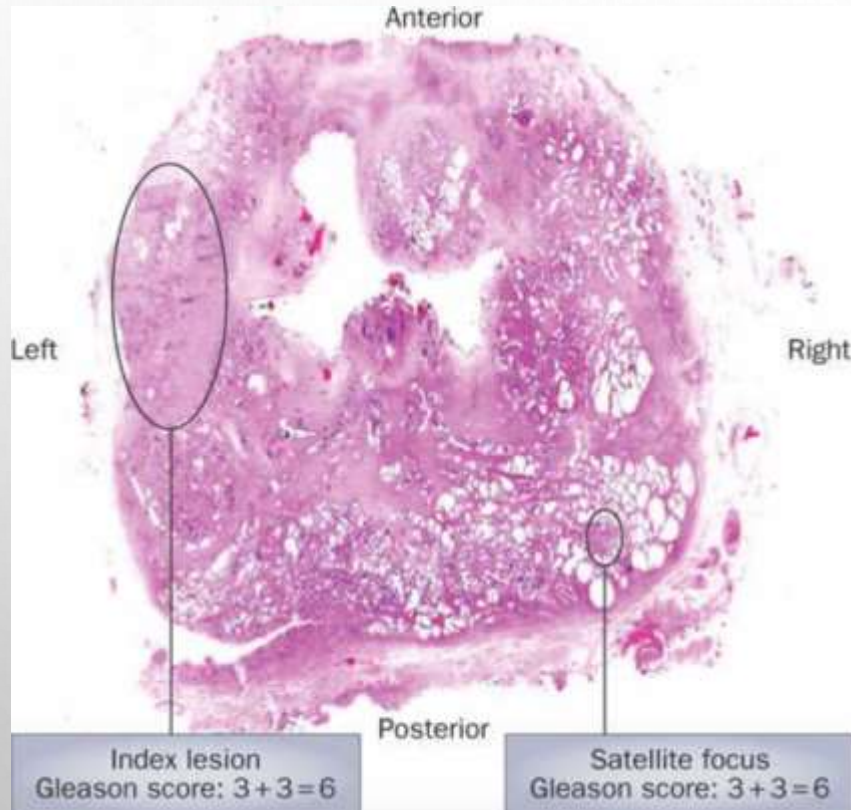
80% Multifocalidad
1/3 unilateral
Lesión Index

“NO TODOS LOS TUMORES EN
LA PRÓSTATA SE
COMPORTAN SIMILAR”



- Mouraviev V, Mayes JM, Madden JF, Sun L, Polascik TJ. Analysis of laterality and percentage of tumor involvement in 1386 prostatectomized specimens for selection of unilateral focal cryotherapy. *Technol Cancer Res Treat* 2007;6:91–5.
- Bott SR, Ahmed HU, Hindley RG, Abdul-Rahman A, Freeman A, Emberton M. The index lesion and focal therapy: an analysis of the pathological characteristics of prostate cancer. *BJU Int* 2010;106: 1607–11.

LOCALIZACIÓN Y LESIÓN A TRATAR



LESIÓN INDEX
Foco dominante medido
por volumen

Altera la historia natural
Clínicamente significativo

- Markos Karavitis, Hashim U. Ahmed, Paul D. Abel, Steven Hazell & Mathias H. Winkler. Tumor focality in prostate cancer: implications for focal therapy. Nature Reviews Clinical Oncology 8, 48-55 (January 2011)

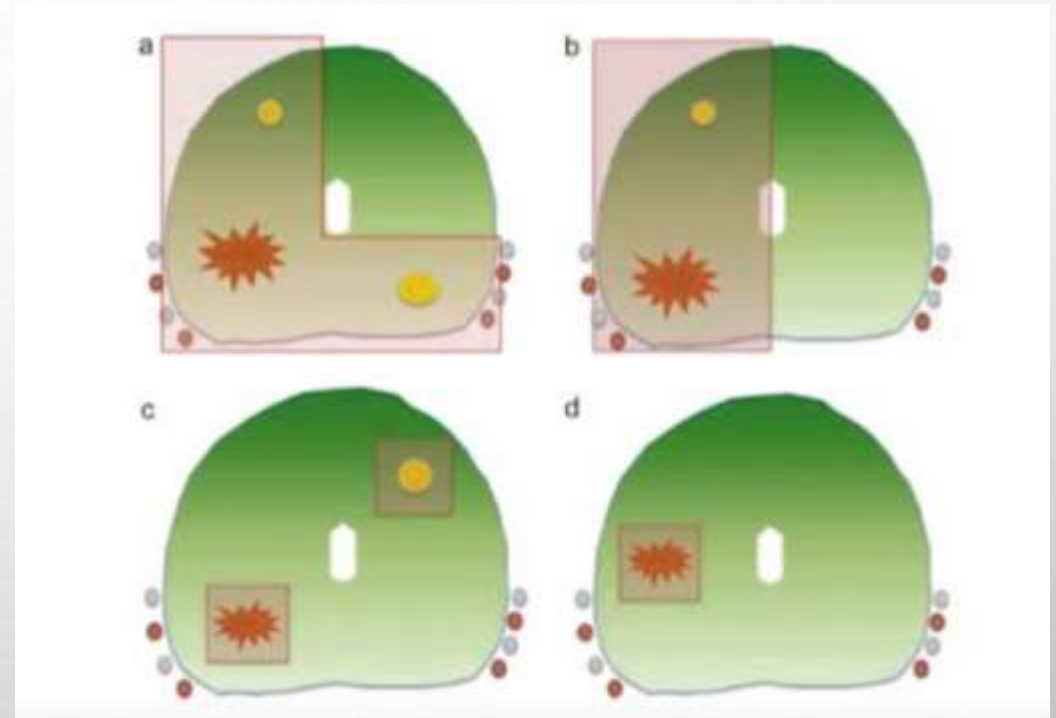
CÁNCER DE PRÓSTATA LOCALIZADO

LOCALIZACIÓN Y LESIÓN A TRATAR

POSTERIOR – HIFU

APICAL – BRAQUITERAPIA

ANTERIOR – “NEEDLE THERAPIES”



- E. Barret, R. Ganzer, G. Salomon, M. Fielfer et al. “Future of focal therapy for the treatment of Prostate Cancer European section of urotechnology (ESUT) position”. Arch. Esp. Urol. 2019;72 (2):167-173.

CÁNCER DE PRÓSTATA LOCALIZADO

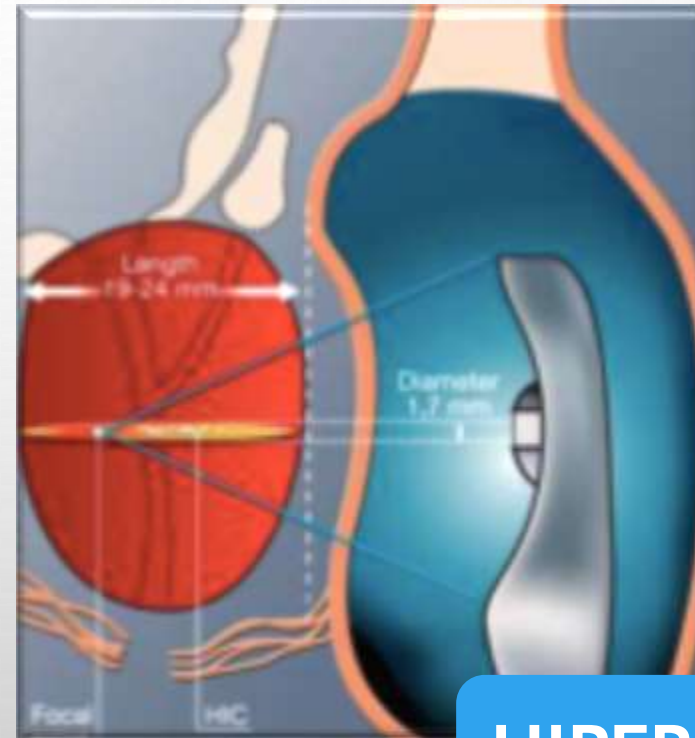
LOCALIZACIÓN DE LA ENFERMEDAD

- NO HAY CONSENSO DE CUÁNTAS BIOPSIAS SON SUFICIENTES PARA DETECTAR LA MAYORÍA DEL CÁNCER DE PRÓSTATA.
- GOLD STANDARD: BIOPSIA DE MAPEO POR PLANTILLA TRANSPERINEAL
 - MARCO DE MUESTREO CADA 5MM
 - IMPRECISIÓN DE LA BIOPSIA ULTRASONOGRÁFICA TRANSRECTAL
- Washington SI, Bonham M, Whitson JM, Cowan JE, Carroll PR. "Transrectal ultrasonography-guided biopsy does not reliably identify dominant cancer location in men with low-risk prostate cancer". BJU Int 2012;110:50-5.
- Hossak T, Patel MI, Huo A, et al. "Location and pathological characteristics of cancers in radical prostatectomy specimens identified by transperineal biopsy compared to transrectal biopsy". J. Urol 2012;188:781-5.

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

- FRECUENCIA 0.8 A 3.5 MHZ
- MECANISMO:
 - CONVERSIÓN DE ENERGÍA MECÁNICA A CALOR.
 - CAVITACIÓN INERTE.
- ONDAS ULTRASÓNICAS QUE GENERAN TEMPERATURAS $> 80^{\circ}$.
 - NECROSIS COAGULATIVA IRREVERSIBLE.



HIPERTERMIA

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)



Sonablate-500
Focu Surgery (Indianapoli, US)

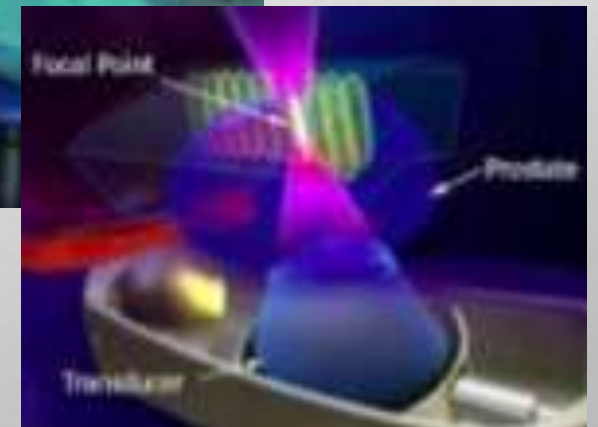


Ablatherm
EDAP TMS (Lyons, France)

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

- TÉCNICA
 - TRANSRECTAL EN TIEMPO REAL
 - CALENTAR 3 SEGUNDOS Y ENFRIAR 6 SEGUNDOS
 - <60% DE LA PRÓSTATA A TRATAR.
 - >10MM DE LOS PEDÍCULOS NEUROVASCULARES.
- **LIMITACIONES: RTUP PREVIO A HIFU**
 - PRÓSTATAS >40-50CC.
 - ZONA ANTERIOR DE LA PRÓSTATA.



CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

- 402 PACIENTES, T1-2 N0-X M0, GLEASON 5 A 7 (77.5%)
- VOLUMEN PROSTÁTICO 28.0 +/- 13.8 ML
- PSA 10.9 +/- 8.7 NG/ML
- SEGUIMIENTO 58 SEMANAS.
- **BIOPSIA NEGATIVA 87.2%.**
 - 92.1% CON PSA NADIR 1.3 NG/ML EN GRUPO DE BAJO RIESGO

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

- RESULTADOS A LARGO TÉRMINO

- SOBREVIVENCIA A 5 AÑOS LIBRE DE ENFERMEDAD 83%, 53% Y 36% EN GRUPOS DE BAJO, INTERMEDIO Y ALTO RIESGO.

- SOBREVIVENCIA A 5 AÑOS LIBRE DE ENFERMEDAD EN GRUPO DE BAJO E INTERMEDIO RIESGO FUE 66%.

- 28% FALLA DEL TRATAMIENTO EN PACIENTES DE BAJO RIESGO .

- Gelet, J.Y. Chapelon, L. Poissonier et al., "Prostate cancer control with transrectal HIFU in 242 consecutive patients: 5-year results" European Urology, vol. 3, supplement, p. 214, 2004.
- A. Blana, F.J. Mrat, B. Walter et al., "First analysis of the longterm results with transrectal HIFU in patients with localized prostate cancer" European Urology, vol. 53, nº 6, pp.1194.1203, 2008.

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

- EL ÚNICO ESTUDIO RANDOMIZADO RECLUTÓ PACIENTES DE BAJO RIESGO.
- ESTUDIO MULTICÉNTRICO – COHORTE:
 - SEGUIMIENTO A 5 AÑOS.
 - 625 PACIENTES DESDE 2006 A 2015.
 - GLEASON 6-9. *GLEASON 6 – REQUIERE UN TUMOR ≥ 4 MM.
 - T1C-3BN0M0.
 - PSA ≤ 30 NG/ML



- S. Guillaumier, M. Peters, M. Arya et al. “A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer” European urology 74 (2018);422-429. <https://doi.org/10.1016/j.eururo.2018.06.006>

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

- 505/625 PACIENTES RIESGO INTERMEDIO. (84%)
- ÉXITO 88%; LIBRE DE MTS 98%; SUPERVIVENCIA CÁNCER ESPECÍFICA 100%; SUPERVIVENCIA GLOBAL 99%.
- PANEL DE EXPERTOS →
 - TF EN RIESGO BAJO-INTERMEDIO SEGÚN D'AMICO.

ORIGINAL ARTICLE

NEW PARADIGMS IN PROSTATE CANCER - TREATMENT

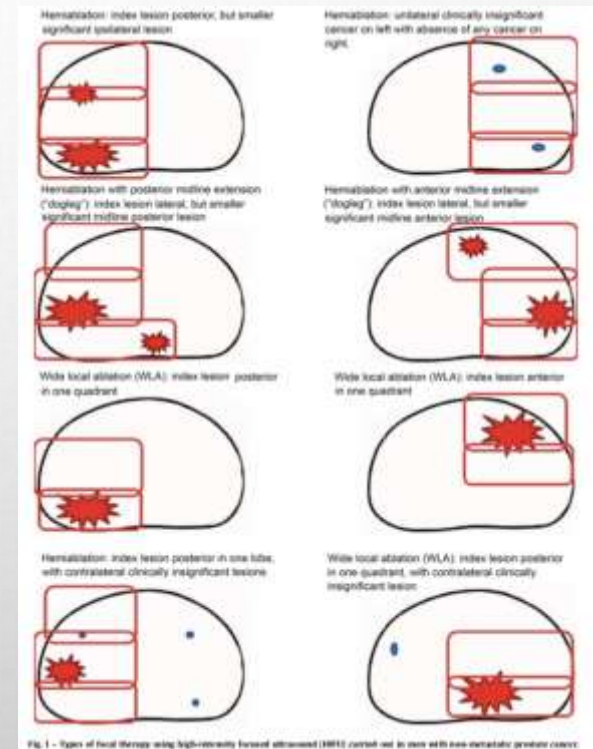
Arch. Esp. Urol. 2019; 72 (2): 167-173

**FUTURE OF FOCAL THERAPY FOR THE TREATMENT OF PROSTATE CANCER-
EUROPEAN SECTION OF UROTECHNOLOGY (ESUT) POSITION**

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

- DURANTE EL SEGUIMIENTO:
 - PSA CADA 3-6 MESES.
 - RMMP DE PRÓSTATA CADA AÑO. \uparrow VPN (>95%).
 - CUESTIONARIOS: IPSS ; EPIC.
- 2 ELEVACIONES CONSECUTIVAS DEL PSA NADIR – NUEVA BIOPSIA.
- COMO 2º TTO SE OFRECIÓ NUEVA HIFU, PROSTATECTOMÍA RADICAL O RT.



- S. Guillaumier, M. Peters, M. Arya et al. "A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer" European urology 74 (2018);422-429. <https://doi.org/10.1016/j.eururo.2018.06.006>

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

3.1. *Baseline demographics*

A total of 625 patients were treated with focal HIFU, of whom 599 reached at least 6-mo follow-up and 505 (84%) had intermediate- or high-risk prostate cancer (Table 1). Table 2 lists the biopsy characteristics. When excluding patients with an event ($n = 60$) the median follow-up was 56 mo (IQR 35–70).

3.2. *Primary outcome*

The FFS at 1, 3, and 5 yr was 99% (95% CI 98–100%), 92% (95% CI 90–95%), and 88% (95% CI 85–91%), respectively (Table 3). Kaplan-Meier estimates at 5 yr were 96% (95% CI 91–100%), 88% (95% CI 84–93%), and 84% (95% CI 78–90%) for low-, intermediate, and high-risk groups, respectively (Table 3 and Fig. 2).

4. Discussion

Our study shows that following focal HIFU, failure-free survival was 88% at 5 yr. Metastasis-free survival was 98% and cancer-specific survival was 100% at 5 yr. Only 2% had urinary incontinence requiring use of one daily pad and no men required more than 1 pad/d. Bowel complications were rare (0.3%).

- S. Guillaumier, M. Peters, M. Arya et al. "A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer" *European urology* 74 (2018);422-429. <https://doi.org/10.1016/j.eururo.2018.06.006>

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

Advantages

Noninvasive (no needles in prostate)

With MRI, precise localization of target, real-time monitoring of treatment effects with thermography, documentation of treated area with intravenous contrast

Can be repeated

Outpatient procedure, with little time lost from normal activities

Low morbidity

Does not preclude subsequent radical therapy, but this could be more difficult

Disadvantages

Heat risks permanent damage to erectile nerves

Without MRI, real-time monitoring of treatment effect not possible

With MRI, is expensive and requires multidisciplinary collaboration

Difficult to reach anterior prostate

Changes morphology of prostate, making follow-up with digital rectal examination or imaging more difficult

No experience with HIFU for focal therapy

- Marberger M, Carroll PR, Zelefsky MJ, Coleman JA, Hricak H, Scardino PT, Abenham LL, "New treatments for localized prostate cancer" Urology. 2008 Dec; 72 (6 Suppl):S36-43.

LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

- “NO HAY BUENA CALIDAD DE EVIDENCIA EN LA EFICACIA Y SEGURIDAD”.
 - FALTA DE ESTUDIOS RANDOMIZADOS BIEN DISEÑADOS.
- “MUY VARIABLE LA TASA LIBRE DE PROGRESIÓN BIOQUÍMICA Y COMPLICACIONES REPORTADAS”

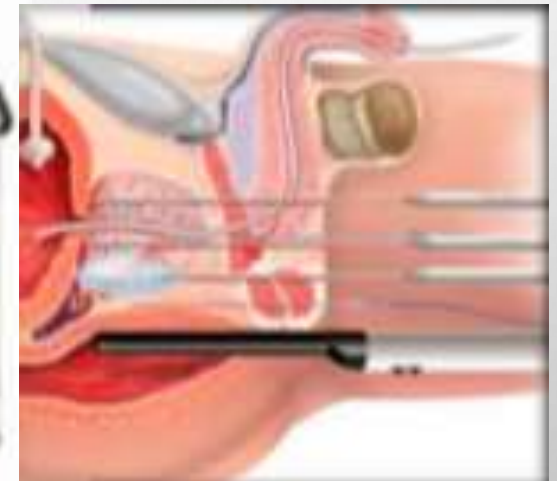
Biopsias negativas 35–95%

Sobrevida libre de enfermedad
a 5 años 61.2–95%

- Cordeiro ER, Cathelineau X, Thüroff S, Marberger M, Crouzet S, de la Rosette JJ. “High-intensity focused ultrasound (HIFU) for definitive treatment of prostate cancer” BJU Int. 2012 Nov; 110 (9):1228-42.

CANCER DE PROSTATA LOCALIZADO CRIOTERAPIA

- USO DE ULTRASONIDO EN TIEMPO REAL PARA MONITORIZAR EL PROCESO DE ENFRIAMIENTO.
- NECROSIS ISQUÉMICA Y COAGULATIVA. ACCESO TRANSPERINEAL.
- CALENTADOR URETRAL CON SISTEMA DE IRRIGACIÓN CONTINUA.



- Takeo Nomura and Hiromitsu Mimata. "Focal Therapy in the Management of Prostate Cancer: An Emerging Approach for Localized Prostate Cancer". Advances in Urology. Volumen 2012, doi:10.1155/2012/391437.

CANCER DE PROSTATA LOCALIZADO CRIOTERAPIA

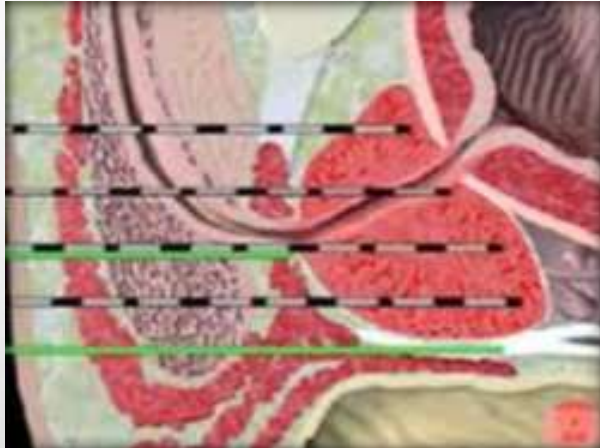
- GAS ARGÓN PARA CONGELAR
- GAS HELIO PARA CALENTAR

- CONTRAINDICACIÓN:
 - CÁNCER CERCANO A URETRA
 - STUI SEVERO O RTUP PREVIA
 - TAMAÑO DE PRÓSTATA >50CC.



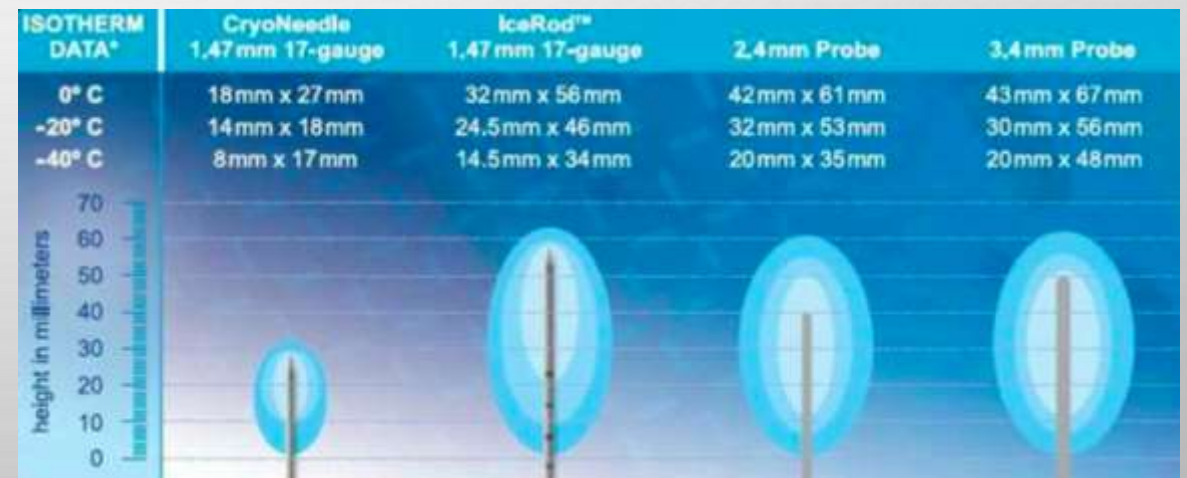
CANCER DE PROSTATA LOCALIZADO

CRIOTERAPIA



Parámetros (-40°C por 2 ciclos):

- Tasa de enfriamiento
- Temperatura más baja
- Duración del ciclo de enfriamiento



CANCER DE PROSTATA LOCALIZADO CRIOTERAPIA



- 70 PACIENTES
- 56% T1C Y 43% T2A; GLEASON 3+3 41% Y 3+4 34%;
- 67% RIESGO INTERMEDIO
- VOLUMEN PROSTÁTICO PROMEDIO 38 ML
- ÍNDICE DE LESIÓN VISIBLE EN ULTRASONIDO 85%
- PSA PRETRATAMIENTO 5.4NG/ML, ↓70% A 1.6NG/ML
- BIOPSIA PROSTÁTICA NEGATIVA 75%
- CONTINENCIA 100% Y POTENCIA 86%

CANCER DE PROSTATA LOCALIZADO CRIOTERAPIA

Onik G al. "Male lumpectomy": focal therapy for prostate cancer using cryoablation. Urology. 2007;70(suppl 1):S16-S21.

Autor / Publicación	Nº pacientes	T. Seguimiento (años)	SLEB	Criterio fracaso	Lesión rectal	Incontinencia	Potencia sexual	Biopsias +
Bahn (Endourology, 2006)	31	6	93%	ASTRO	0,0%	0,0%	89%	1,2%
Lambert (Urology, 2007)	25	3	88%	ASTRO II (nadir + 2)	0,0%	0,0%	71%	8% no tratado 4% tratado
Ellis (Urology, 2007)	60	2	80%(1º) 93%(2º)	ASTRO	0,0%	3,6% (6 meses)	71% (12 meses)	23,3% no tratado
Onik (Urol Oncol, 2008)	48	4,5	95%	ASTRO	0,0%	0,0%	90%	4% no tratado 0% tratado
Ellis (Urology, 2007)	112	12	74%	ASTRO	0,0%	0% (24 meses)	51% (6 m) 74% (36 meses)	3,3%

2002 - 2007: > 40% terapia focal (National Cryo-On-Line Data [COLD])

Ward JF.: Classification system: organ Preserving treatment for prostate cancer. Urology 2010; 75 (&):1258-1260

CANCER DE PROSTATA LOCALIZADO CRIOTERAPIA

Advantages	Disadvantages
<p>Good correlation between ice ball and lesion localization</p> <p>Treated lesion (ice ball) visible in real time on ultrasonography</p> <p>Has been used for hemiablation (one lobe) of prostate</p> <p>Morbidity expected to be lower after focal therapy than after treatment of whole gland</p> <p>Can be repeated</p> <p>Does not preclude subsequent radical therapy, but this could be more difficult</p>	<p>Tissue damage extends beyond limit of tissue destruction (risk to surrounding structures)</p> <p>Probe placement is critical</p> <p>Difficult to treat anterior gland</p> <p>Some risk of erectile dysfunction</p> <p>Lack of data on long-term follow-up</p> <p>Changes morphology of prostate, making follow-up with digital rectal examination or imaging more difficult</p>

- Marberger M, Carroll PR, Zelefsky MJ, Coleman JA, Hricak H, Scardino PT, Abenhaim LL. "New treatments for localized prostate cancer". Urology. 2008 Dec;72(6 Suppl):S36-43.

CANCER DE PROSTATA LOCALIZADO TERAPIA FOTODINÁMICA

- FOTSENSIBILIZADOR INTRAVENOSO SOLUBLE (INFUSIÓN 10 MIN) EN VASCULATURA TUMORAL TOOKAD® WST11
 - <60 ML: 4 MG/KG
 - ≥60 ML: 6 MG/KG
- ACTIVACIÓN CON LUZ (20 A 25 MIN) PRODUCE RADICALES DE OXÍGENO QUE PRODUCEN TROMBOSIS VASCULAR
 - LÁSER 753 NM A 150 MW/CM
 - 200 J/CM
- ABORDAJE PERINEAL
- ANESTESIA GENERAL



Derivado
Bacterioclorófilico

CANCER DE PROSTATA LOCALIZADO TERAPIA FOTODINÁMICA

- ⇒ Aplicación fuente energía (luz)
- ⇒ Tejido previamente sensibilizado (tisular/vascular)
- ⇒ Presencia de oxígeno
- ⇒ Radicales libres y derivados del oxígeno
- ⇒ Necrosis tisular por daño vascular y citotóxico – Reacción inflamatoria
- ⇒ Efecto en relación con concentración fármaco y luz de forma simultanea

CANCER DE PROSTATA LOCALIZADO TERAPIA FOTODINÁMICA

BJU Int 2013; 112: 766–774

BJUI
BJU International

TOOKAD[®] Soluble vascular-targeted photodynamic (VTP) therapy: determination of optimal treatment conditions and assessment of effects in patients with localised prostate cancer

Abdel-Rahmène Azzouzi¹, Eric Barret², Caroline M. Moore³, Arnaud Villers⁴, Clare Allen³, Avigdor Scherz⁵, Gordon Muir⁶, Michel de Wildt⁷, Neil J. Barber⁸, Souhil Lebdai¹ and Mark Emberton³

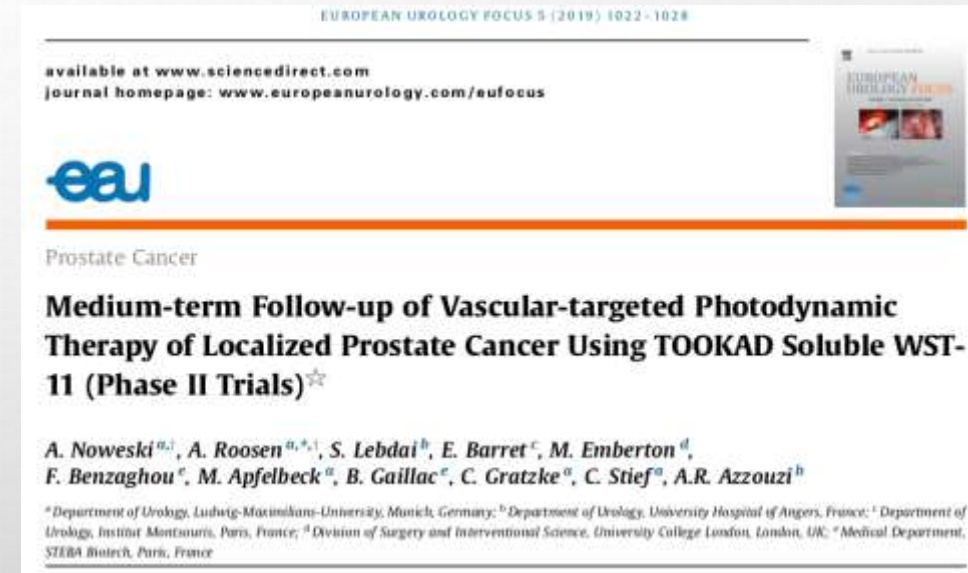
¹University Hospital, Angers, France, ²Institut Mutualiste Montsouris (IMM), Paris, France, ³University College London Hospital, London, UK, ⁴University Hospital of Lille, Lille, France, ⁵Plant Sciences, Weizmann Institute of Science, Rehovot, Israel, ⁶Kings College Hospital, London, UK, ⁷Catharina Hospital, Eindhoven, The Netherlands, and ⁸Frimley Park Hospital, Surrey, UK

CANCER DE PROSTATA LOCALIZADO TERAPIA FOTODINÁMICA

- 85 PACIENTES FASE II
- T2B, 95.3% GLEASON 3+3 (PATRÓN 4 CON \leq 3 CILINDROS POSITIVOS/LÓBULO Y \leq 3 MM LONGITUD MÁXIMA DE CÁNCER EN EL CILINDRO), PSA \leq 10 NG/ML.
- 4 MG/KG TOOKAD[®] + 200 J/CM LUZ (UNILATERAL)
 - A LOS 6 MESES, 83% CON BIOPSIA NEGATIVA (95% CI 68.6–92.2%; P < 0.001).
- A LOS 7 DÍAS, 78% DE NECROSIS PROSTÁTICA EN MRI.
 - EXTRAPROSTÁTICA 76% SIN CONSECUENCIAS CLÍNICAS.
- DISMINUYE EL PSA DEL BASAL -1.01, 2.10 Y -2.20 NG/ML A LOS 1, 3 Y 6 MESES.

CANCER DE PROSTATA LOCALIZADO TERAPIA FOTODINÁMICA

- 68 PACIENTES FASE II
- 4 MG/KG TOOKAD® + 200 J/CM LUZ (UNILATERAL)
 - A LOS 6 MESES, 75% CON BIOPSIA NEGATIVA.
- 10/68 BIOPSIAS POSITIVAS EN AMBOS LÓBULOS. 81% FUERON TRATADOS UNILATERALMENTE.
- A LOS 6 MESES – REDUCCIÓN DEL PSA -2.64 (-2.8 NG/ML).
- A LOS 3.5 AÑOS: ÉXITO EN EL 75%.
- A. Noweski, A. Roosen et al. "Medium-term Follow-up of Vascular-targeted Photodynamic Therapy of Localized Prostate Cancer Using TOOKAD Soluble WST-11 (Phase II Trials). European Urology Focus 5 (2019);1022-1028.



CÁNCER DE PRÓSTATA LOCALIZADO TERAPIA FOCAL

- AZZOUZI ET AL. → ESTUDIO FASE 3. ENSAYO RANDOMIZADO QUE COMPARA LA TERAPIA FOTODINÁMICA CON LA VIGILANCIA ACTIVA.
 - SUPERIORIDAD DE LA TERAPIA FOTODINÁMICA EN EL RETRASO DE UN TERAPIA RADICAL.
 - ***LA MAYORÍA DE PACIENTES QUE RECIBIERON TF ERAN CANDIDATOS A VA.

NEW PARADIGMS IN PROSTATE CANCER - TREATMENT

ORIGINAL ARTICLE

Arch. Esp. Urol. 2019; 72 (2): 167-173

FUTURE OF FOCAL THERAPY FOR THE TREATMENT OF PROSTATE CANCER- EUROPEAN SECTION OF UROTECHNOLOGY (ESUT) POSITION

Eric Barret¹, Roman Ganzer², Georg Salomon³, Marcel Fielder⁴, Antonio Celia⁵, Dmitry Enikeev⁶, Juan Ignacio Martínez-Salamanca⁷, Evangelos Liatsikos⁸ and Juan Gómez Rivas⁹.

CANCER DE PROSTATA LOCALIZADO TERAPIA FOTODINÁMICA

Table 2 – Adverse events.

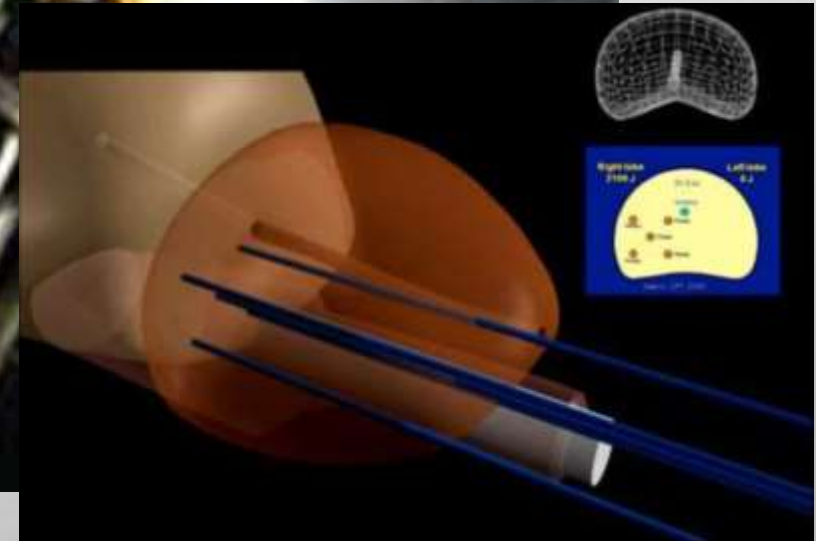
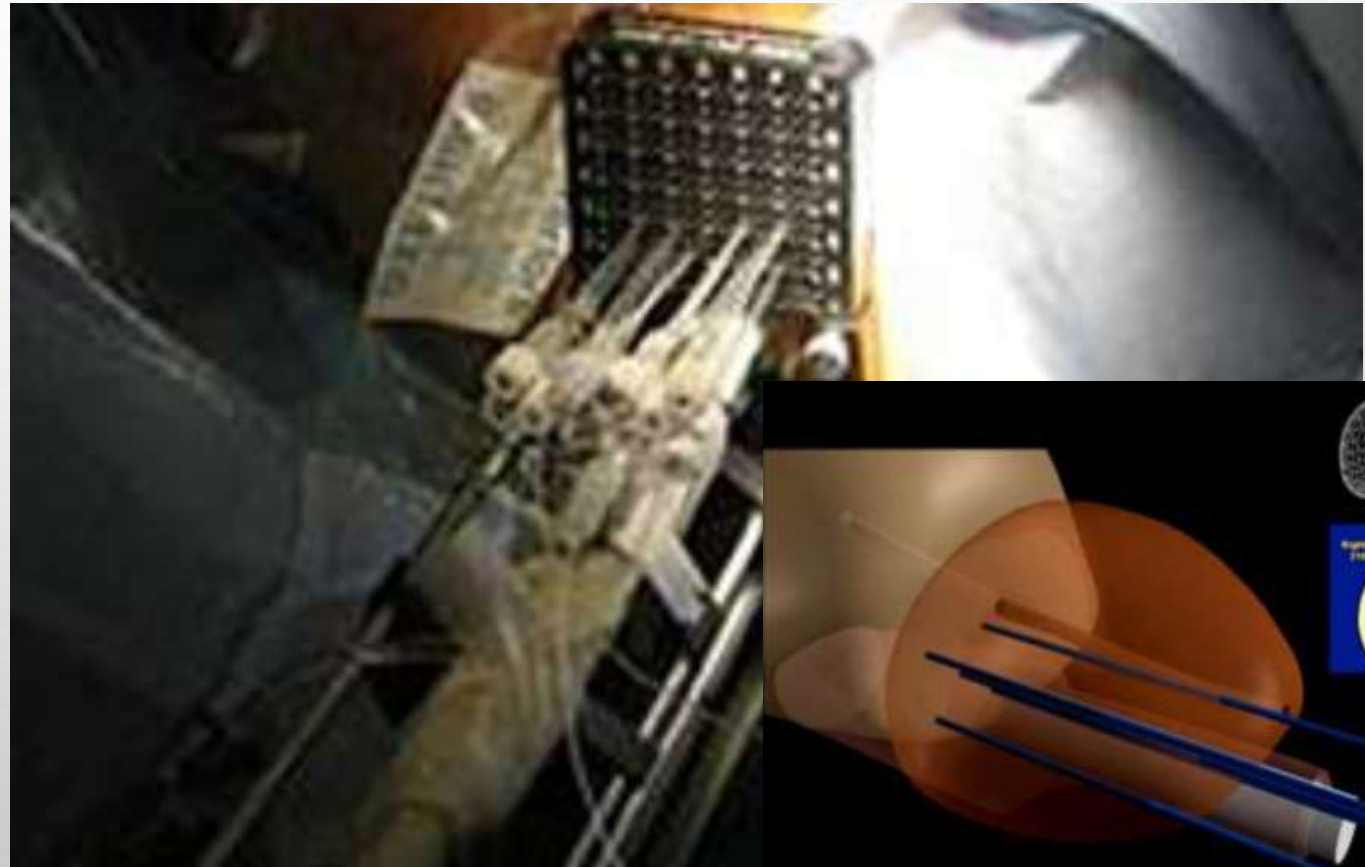
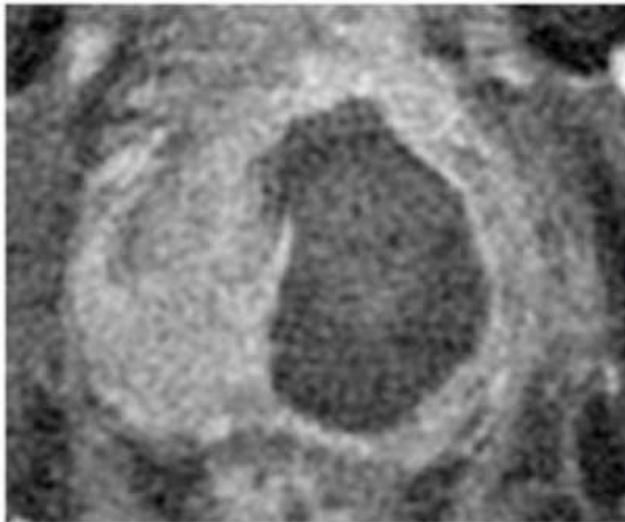
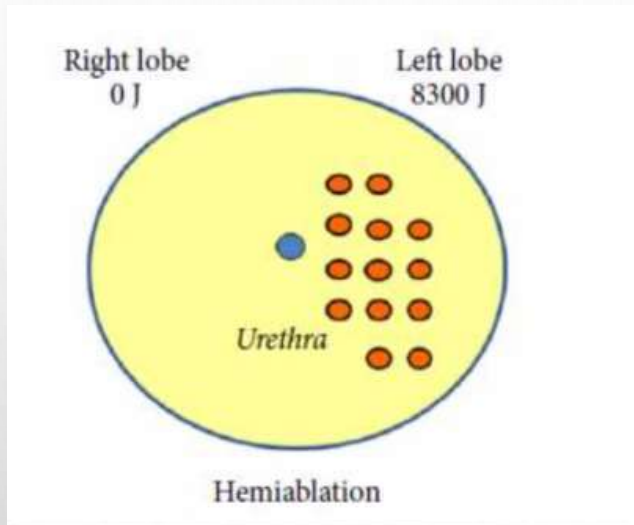
TEAES	<i>n</i>	%	Clavien I	Clavien II	Clavien III	Clavien IV-V
Erectile dysfunction	28	44	0	28	0	0
Ejaculation sequelae	5	8	5	0	0	0
Decreased libido	4	6	4	0	0	0
LUTS	14	22	12	0	2	0
Macroscopic hematuria	1	2	1	0	0	0
Urinary infection	2	3	0	2	0	0
Perineal pain	9	14	9	0	0	0
Urethral stenosis	1	2	0	0	1	0
Total TEAES	64	100	31	30	3	0
Nonrelated AE	20	–	–	–	–	–
Total AE	84	–	–	–	–	–

AE = adverse events; LUTS = lower urinary tract syndrome; TEAES = treatment emergent AEs.

- A. Noweski, A. Roosen et al. “Medium-term Follow-up of Vascular-targeted Photodynamic Therapy of Localized Prostate Cancer Using TOOKAD Soluble WST-11 (Phase II Trials). *European Urology Focus* 5 (2019);1022-1028.

CANCER DE PROSTATA LOCALIZADO

TERAPIA FOTODINÁMICA



CANCER DE PROSTATA LOCALIZADO TERAPIA FOTODINÁMICA

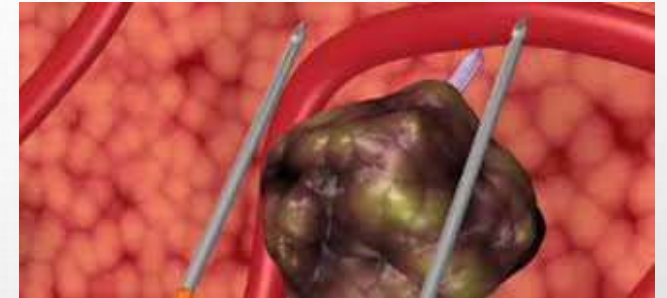
Advantages	Disadvantages
<p data-bbox="461 578 1370 649">Outpatient procedure with minimal capital expense (setup similar to that for brachytherapy)</p> <p data-bbox="461 685 1014 721">Does not change morphology of prostate</p> <p data-bbox="461 756 1370 828">Good tissue penetration (treatment of relatively large tumor volume)</p> <p data-bbox="461 863 667 899">Low morbidity</p> <p data-bbox="461 935 1370 1006">Compared with previous photodynamic agents, WST09 is rapidly metabolized and eliminated, resulting in no photosensitivity issues</p> <p data-bbox="461 1042 682 1078">Can be repeated</p> <p data-bbox="461 1113 1370 1185">Does not preclude subsequent radical therapy, but this could be more difficult</p>	<p data-bbox="1600 578 2018 614">Difficult to treat anterior gland</p> <p data-bbox="1600 649 2229 721">Limited clinical experience, lack of data on long-term outcomes</p> <p data-bbox="1600 756 2229 828">Photodynamic agent may be thrombogenic, requires prophylactic heparin for procedure</p> <p data-bbox="1600 863 2221 899">Novel technology requires specific equipment</p>

- Marberger M, Carroll PR, Zelefsky MJ, Coleman JA, Hricak H, Scardino PT, Abenhaim LL. "New treatments for localized prostate cancer". Urology. 2008 Dec;72(6 Suppl):S36-43.

CANCER DE PROSTATA LOCALIZADO

ELECTROPORACIÓN IRREVERSIBLE

- ⇒ Pulsos eléctricos NO térmicos
- ⇒ Crea poros irreversibles en la membrana celular
- ⇒ Aplicación local de pulsos repetitivos de forma transperineal
- ⇒ El número de aguas será directamente proporcional al tamaño de la lesión



LOCALIZADO MORBILIDAD DE LA TERAPIA FOCAL

EUROPEAN UROLOGY 63 (2013) 618–622

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



European Association of Urology



Platinum Priority – Prostate Cancer

Editorial by Ben J. Challacombe and Declan G. Murphy on pp. 623–624 of this issue

Morbidity of Focal Therapy in the Treatment of Localized Prostate Cancer

Eric Barret^{a,}, Youness Ahallal^a, Rafael Sanchez-Salas^a, Marc Galiano^a, Jean-Marc Cosset^a, Pierre Validire^b, Petr Macek^a, Matthieu Durand^a, Dominique Prapotnich^a, François Rozet^a, Xavier Cathelineau^a*

^a Urology Service, Department of Surgery, Institut Mutualiste Montsouris, Paris, France; ^b Department of Pathology, Institut Mutualiste Montsouris, Paris, France

LOCALIZADO MORBILIDAD DE LA TERAPIA FOCAL

- 106 PACIENTES 66.5AÑOS
- 91 T1C, GLEASON 3+3, PSA 6.1 NG/ML, PRÓSTATA 63 G
- 47% CRIOTERAPIA, 22% VTP, 20% HIFU, 11% BRAQUITERAPIA
- 13% COMPLICACIONES RELACIONADAS AL TRATAMIENTO
 - 10% GRADO 1: RETENCIÓN URINARIA, DOLOR PÉLVICO
 - 1% GRADO 2: HEMATURIA MACROSCÓPICA
 - 2% GRADO 3B: FÍSTULA RECTAL CON ABCESO PERIANAL, ESTRECHEZ URETRAL
- MAYORÍA DE COMPLICACIONES CON CRIOTERAPIA
- <2% COMPLICACIONES MAYORES

LOCALIZADO

MORBILIDAD DE LA TERAPIA FOCAL

Table 2 – Preliminary oncologic and functional results

Energy modality	PSA, ng/ml, median (IQR)				IPSS, median (IQR)		IIEF-5, median (IQR)	
	Baseline	3 mo	6 mo	12 mo	Baseline	12 mo	Baseline	12 mo
Cryotherapy	6.2 (5.0–7.9)	2.9 (2.0–5.0)	2.8 (1.2–4.6)	2.5 (0.9–4.4)	9 (3–10)	5 (1–11)	19 (9–25)	14 (8–25)
Brachytherapy	6.2 (5.4–7.5)	3.3 (2.5–5.7)	3.2 (2.0–5.1)	2.8 (1.2–4.7)	3 (1–7)	7 (2–12)	21 (10–25)	14 (8–24)
VTP	5.7 (4.8–6.7)	3.0 (2.2–4.9)	2.8 (1.1–4.4)	3.2 (2.1–4.7)	6 (2–9)	6 (3–10)	23 (17–25)	13 (7–25)
HIFU	6.0 (5.1–8.1)	2.7 (1.8–4.7)	3.1 (2.1–5.3)	3.1 (2.4–4.3)	3 (1–7)	6 (2–11)	20 (15–25)	14 (8–25)

PSA = prostate-specific antigen; IQR = interquartile range; IPSS = International Prostate Symptom Score; IIEF-5 = International Index of Erectile Function; VTP = vascular-targeted photodynamic therapy; HIFU = high-intensity focused ultrasonography.

CANCER DE PRÓSTATA LOCALIZADO

ULTRASONIDO FOCALIZADO DE ALTA INTENSIDAD (HIFU)

Complicaciones más comunes:

Complication	Median (range) %	n*
HIFU as primary treatment		
Urinary retention	5.3 (<1–8.8)	1185
Urinary tract infection	7.5 (1.8–47.9)	3071
Urethrorectal fistula	1.0 (0–2.7)	2692
Urethral stricture	12.3 (1.8–24)	712
Stenosis (urethra, bladder, neck)	7.8 (<1–17)	1171
Urinary incontinence (any degree)	8.1 (<1–34)	3803
Infravesical obstruction	17 (13.6–24.5)	575
Chronic perineal pain	3.4 (0.9–13.4)	1233
Impotence†	44 (20–77)	611
Epididymitis	6.1 (3.2–8.3)	316
Prostatitis	6.2 (5.6–6.8)	180

1. Disfunción eréctil 20–81.6%
2. Infección del tracto urinario 1.8–47.9%
3. Incontinencia urinaria <1–34.3%
4. Retención urinaria <1–20%

RTUP concomitante para reducir morbilidad asociada al tratamiento

• Lukka H, Waldron T, Chin J, Mayhew L, Warde P, Winkvist E, Rodrigues G, Shayegan B; Genitourinary Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. High-intensity focused ultrasound for prostate cancer: a systemic review. Clin Oncol (R Coll Radiol). 2011 Mar, 23 (2):117-27.

CANCER DE PROSTATA LOCALIZADO TERAPIA FOTODINÁMICA

- 87% EFECTOS ADVERSOS:
 - 61% AL FÁRMACO Y 64% AL DISPOSITIVO DE ESTUDIO
 - DISURIA 34%
 - INFECCIÓN DEL TRACTO URINARIO 24%
 - RETENCIÓN URINARIA 13%
 - CONSTIPACIÓN 13%
 - DOLOR PERINEAL 12%
 - 9% SERIAS: PROSTATITIS, HEMATURIA, EPIDÍDIMO- ORQUITIS, ESTRECHEZ EN URETRA PROSTÁTICA, QUISTE PROSTÁTICO INFLAMATORIO, NEUROPATÍA ÓPTICA ISQUÉMICA

LIMITACIONES DE LA TERAPIA FOCAL EN CÁNCER DE PRÓSTATA LOCALIZADO

LOCALIZADO CONTROVERSIAS EN LA TERAPIA FOCAL

Validez teórica de la lesión índice

Tecnología ablativa para su aplicación

Diseño de estudios evaluativos reciente

Murphy DG, Walton TJ, Connolly S, Costello AJ. Focal therapy for localised prostate cancer: are we asking the correct research questions? BJU Int 2012;109:1-3.

CÁNCER DE PRÓSTATA LOCALIZADO

CONTROVERSIAS EN LA TERAPIA FOCAL

ES UN TRATAMIENTO LOCAL
EXPERIMENTAL...
MULTIFOCALIDAD DEL CÁNCER



- Barret, E. Ganzer, R, Salomon, G. et al. "FUTURE OF FOCAL THERAPY FOR THE TREATMENT OF PROSTATE CANCER-EUROPEAN SECTION OF UROTECHNOLOGY (ESUT) POSITION". Arch. Esp. Urol 2019; 72 (2): 167-173.

CÁNCER DE PRÓSTATA LOCALIZADO

LIMITACIONES DE LA TERAPIA FOCAL

Table 1 – Percentage of bilateral disease in recent prostatectomy series⁷

Study	Pathologic protocol	No. of patients	Percentage of bilateral-multifocal disease
Noguchi et al [15]	Stanford protocol	222	76
Song et al [16]	Whole-mounted	132	33
Ng et al [17]	Whole-mounted	364	85
Eichelberger et al [18]	Whole-mounted	312	85
Scales et al [19]	Whole-mounted	261	65
Tareen et al [20]	NA	1467	79
Mouraviev et al [21]	3-mm intervals	1184	81

CÁNCER DE PRÓSTATA LOCALIZADO

LIMITACIONES DE LA TERAPIA FOCAL

Table 1 – Theoretical possibilities and limitations of focal therapy for prostate cancer

Possibilities	Limitations
Ablation of cancer foci with noninferior rates of cancer progression or metastases compared to surgery or radiation Minimizing risk or severity of treatment-related morbidity	Inadequate cancer ablation
Ability to retreat the prostate with focal or whole-gland interventions	Incomplete tumor characterization due to suboptimal clinical staging, mapping, and imaging Unknown impact of untreated nonindex lesions Posttreatment monitoring of cancer status without validated definitions of clinical failure Debatable cost effectiveness

LOCALIZADO

CANDIDATO IDEAL PARA LA TERAPIA FOCAL

Tabla 1 Criterios de selección de pacientes candidatos a terapia focal

Clinico

Estadio clínico T1 o T2a

PSA < 10 ng/ml

Densidad de PSA < 0,15 ng/ml/cc³

Velocidad de PSA < 2 ng/ml anual durante el año previo al diagnóstico

Biopsia

Mínimo 12 cores

No Gleason grado 4 o 5

Porcentaje máximo de tumor en cada core: 20%

Máxima extensión de tumor en cada core: 7 mm

Porcentaje máximo de cores afectados por tumor: 33%

Imagen

Lesión única con un tamaño máximo: 12 mm

Máxima extensión de contacto capsular: 10 mm

Ausencia de extensión extraprostática o invasión de vesículas seminales

- Gómez-Veiga F, et al. Terapia focal en cáncer de próstata. Racionalidad, indicaciones y selección. Actas Urol Esp. 2014. <http://dx.doi.org/10.1016/j.acuro.2013.12.005>

ÉXITO Y FALLO DE LA TERAPIA FOCAL LOCALIZADO

- NO HAY MEDIDA DE RESULTADO DE PSA VÁLIDO
- UTILIZACIÓN DE CRITERIOS DE FALLA LUEGO DE RADIOTERAPIA

- ASTRO
- PNOENIX
 - VELOCIDAD DE PSA <0.75 NG/ML ANUAL
- STUTTGART (HIFU)
 - $\uparrow 1.2$ NG/ML DEL NADIR

- NECESIDAD DE TRATAMIENTO SECUNDARIO FOCAL 0–34%

PSA postRT \neq PSA post terapia focal

Tejido prostático remanente

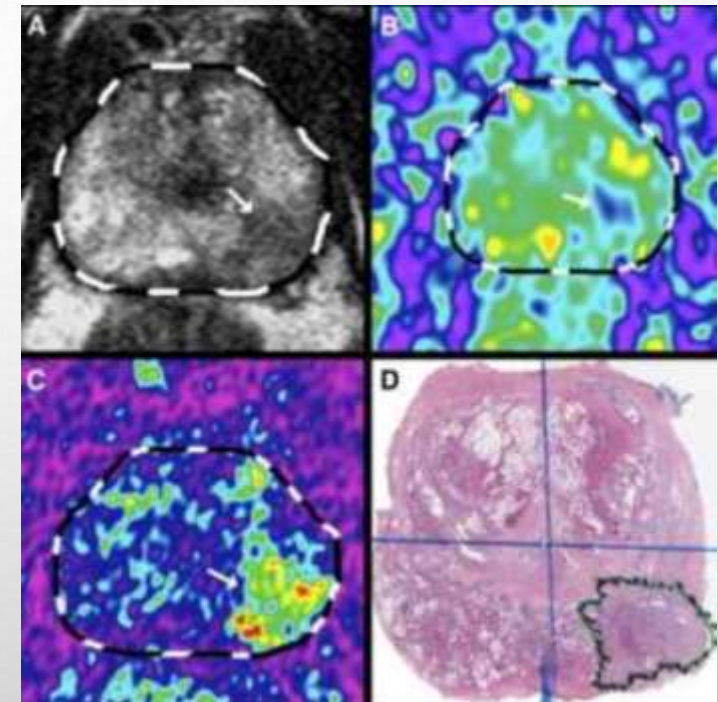
Mecanismo diferente de muerte celular

- Ganzer R, Robertson CN, Ward JF, et al. Correlation of prostatespecific antigen nadir and biochemical failure after high-intensity focused ultrasound of localized prostate cancer based on the Stuttgart failure criteria. BJU Int 2011; 108:E196–201.
- Nguyen PL, Chen MH, Zhang Y, et al. Updated results of magnetic resonance imaging guided partial prostate brachytherapy for favorable risk prostate cancer: implications for focal therapy. J Urol 2012;188:1151–6.

ÉXITO Y FALLO DE LA TERAPIA FOCAL

LOCALIZADO

- TASA DE BIOPSIA PROSTÁTICA POSITIVA
 - 50% TODAS LAS ÁREA
 - 33% ÁREA TRATADA
- CÁNCER RESIDUAL (SEGUIMIENTO 17 A 47 MESES)
 - 8-10% TRUS
 - 44% TTMB



- Losa A, Gadda GM, Lazzeri M, et al. Complications and quality of life after template-assisted transperineal prostate biopsy in patients eligible for focal therapy. *Urology* 2013;81:1291-6.
- Ahmed HU, Hindley RG, Dickinson L, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. *Lancet Oncol* 2012;13:622-32.

Comparison of peri-operative outcomes and complication rates between post-radiation and post-focal ablation groups

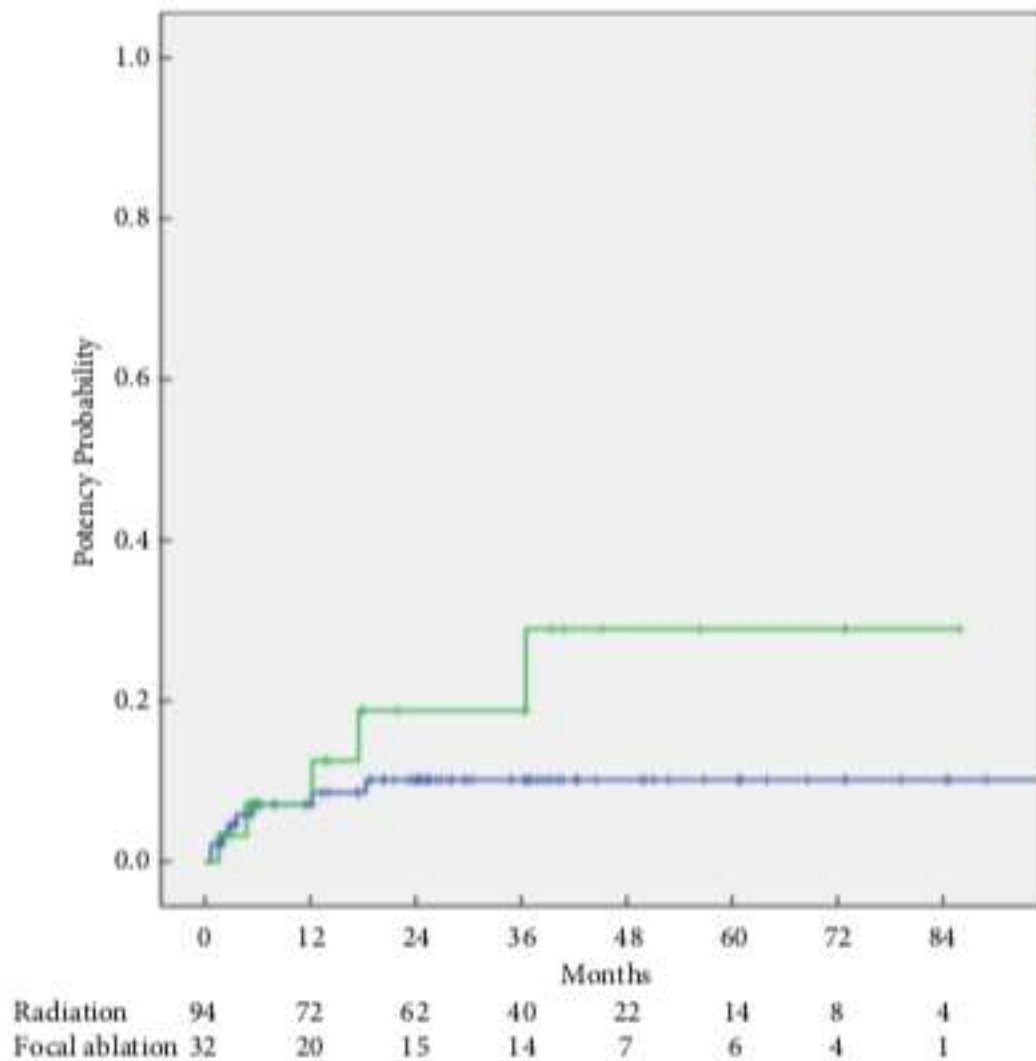
Fikret Fatih O Hariharan Gc
 *Advent Health G USA, and †Depart

Table 4 Comparison of pathological, oncological and functional outcomes between post-radiation and post-focal ablation groups

	Radiation	Focal	P
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Comparison of peri-operative outcomes and complication rates between post-radiation and post-focal ablation groups

Fig. 3 Cumulative probability of potency after salvage robot-assisted laparoscopic prostatectomy by study group (number of patients in the study of groups at each time point is shown at the bottom of the figure).



	Focal ablation group, n = 32	P
	22.38 ± 16.26	0.087
	4.06 ± 12.4	0.958
	2.5 ± 56.09	0.247
	1 (65.6)	0.410
	1 (34.4)	
	.09 ± 0.53	0.289
	0.16 ± 3.7	0.018*
	(15.6)	0.239
	(6.2)	0.355
	9 (90.6)	0.446
	(3.1)	
	(3.1)	
	(3.1)	
	(0)	
	(0)	
	(0)	
	(3.1)	0.678

Potency change at follow-up, n (%)

	Radiation	Focal	P
Patients with good baseline EF (SHIM score 17–25)			
EF unchanged	5 (5.3)	5 (15.6)	0.435
EF deteriorated	33 (35.1)	13 (40.6)	
Patients with poor baseline EF (SHIM score 0–16)			
EF decreased/unchanged	56 (59.5)	14 (43.7)	

n ± SD, unless otherwise indicated. *P < 0.05.

LOCALIZADO

RECOMENDACIONES TERAPIA FOCAL: EAU

Active therapeutic options outside surgery and radiotherapy	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting.	Strong
Only offer focal therapy within a clinical trial setting.	Strong

- N. Mottet (Chair), R.C.N. van den Bergh, E. Briers (Patient Representative), P. Cornford (Vice-chair) et al. "Prostate Cancer: European Association of Urology". 2019.

CANCER DE PRÓSTATA LOCALIZADO

MENSAJES PARA LLEVAR A CASA

- ROL DE TRATAMIENTO ENTRE VIGILANCIA ACTIVA Y TERAPIA RADICAL
- ACTUALMENTE NO HAY ESTUDIOS ALEATORIZADOS QUE DEMUESTREN BENEFICIO CON ALGUNA MODALIDAD DE ENERGÍA SOBRE OTRA
- LIMITACIONES EN LA LOCALIZACIÓN DE LA LESIÓN A TRATAR
- ES UNA POSIBLE ALTERNATIVA POR AHORA EXPERIMENTAL
- SEGUIMIENTO BASADO EN LOS PROTOCOLOS DE VIGILANCIA ACTIVA

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The background is a light gray gradient with several realistic water droplets of various sizes scattered across it. The droplets have highlights and shadows, giving them a three-dimensional appearance. The word "GRACIAS" is centered in the middle of the image in a bold, blue, sans-serif font with a slight drop shadow.

GRACIAS