FOCAL THERAPY OF PROSTATE CANCER: WHERE ARE WE?

MICHAEL MARBERGER
PROFESSOR AND CHAIRMAN
DEPARTMENT OF UROLOGY
MEDICAL UNIVERSITY OF VIENNA
IS TREATMENT OF ENTIRE GLAND NEEDED?
MR GUIDED - HIFU OF BREAST CANCER

COURTESY H. HRICAK
PREREQUISITES FOR SUCCESSFUL FOCAL THERAPY OF PROSTATE CA

- LOCALIZED, UNIFOCAL CANCER OF CLINICAL SIGNIFICANCE
- LESION CAN BE LOCALIZED WITH CLINICAL MEANS
- LESION CAN BE TARGETED AND ABLATED AT LOW MORBIDITY
- COMPLETE ABLATION CAN BE MONITORED
PREREQUISITES FOR SUCCESSFUL FOCAL THERAPY OF PROSTATE CA

- LOCALIZED, UNIFOCAL CANCER OF CLINICAL SIGNIFICANCE
1184 RP SPECIMENS - 19.2% "UNILATERAL Ca"

MOURAVIEV, CANCER 110:906, 2007
1184 RP SPECIMENS - 19.2% "UNILATERAL Ca"

MOURAVIEV, CANCER 110:906, 2007
TUMOR VOLUME IN MULTIFOCAL PROSTATE CANCER

Mean volume of 1,832 RP specimens:

- Largest: 2.13 cm³
- 2nd: 0.39 cm³
- 3rd: 0.17 cm³
- 4th: 0.09 cm³
- 5th: 0.04 cm³

OHORI, J. UROL 175 Suppl: 507, 2006
EGGENER, J. UROL 178:2260, 2007
TUMOR VOLUME IN MULTIFOCAL PROSTATE CANCER

1.832 RP SPECIMENS

92% OF EXTRA CAPSULAR EXTENSION COMES FROM THE LARGEST FOCUS

OHORI, J. UROL 175 Suppl: 507, 2006
EGGENER, J. UROL 178:2260, 2007
PROSTATE CA MAINLY MULTIFOCAL
BUT ~ 15-30% UNIFOCAL / UNILATERAL
(PREDOMINANTLY LOW GRADE, LOW VOLUME)
PROSTATE CA MAINLY MULTIFOCAL
BUT ~ 15-30% UNIFOCAL / UNILATERAL
(PREDOMINANTLY LOW GRADE, LOW VOLUME)

WITH MULTIFOCAL CA. OFTEN DOMINATING
INDEX LESION, WHICH DRIVES DISEASE
PROGRESSION ("BIOLOGICALLY UNIFOCAL")
PREREQUISITES FOR SUCCESSFUL FOCAL THERAPY OF PROSTATE CA

- LOCALIZED, UNIFOCAL CANCER OF CLINICAL SIGNIFICANCE

- LESION CAN BE LOCALIZED WITH CLINICAL MEANS
OF 4437 PATIENTS WITH PCa AT TRUS Bx,
158 HAD UNILATERAL, GL. SC. ≤ 6, VOLUME (<5%) PCa AND PSA < 10ng/ml

QUANN, INT.J.CLIN.EXP.PATHOL., 3:401,2010
OF 4437 PATIENTS WITH PCa AT TRUS Bx, 158 HAD UNILATERAL, GL. SC. ≤ 6, VOLUME (<5%) PCa AND PSA < 10ng/ml

↓

AT RADICAL PROSTATECTOMY

74% BILATERAL Ca
31% TU.VOL > 10%
29% GL.SC. > 7

QUANN, INT.J.CLIN.EXP.PATHOL., 3:401,2010
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↓

AT RADICAL PROSTATECTOMY

74% BILATERAL Ca
31% TU.VOL > 10%
29% GL.SC. ≥ 7

MORE CORES TAKEN OR 1 vs. 2 POS. CORES HAD NO IMPACT ON DIAGNOSTIC ACCURACY

QUANN, INT.J.CLIN.EXP.PATHOL., 3:401, 2010
DYNAMIC MULTIPARAMETRIC MR - MRS IMAGING
3T MRI STAGING ACCURACY (vs. RPE SPECIMEN)

46 PATS.

EXPERIENCE > 2 YEARS

BA = BODY ARRAY COIL
3T MRI STAGING ACCURACY (vs. RPE SPECIMEN)

46 PATS.

EXPERIENCE > 2 YEARS

RAD. 1 BAC (0.76)
RAD. 2 BAC (0.61)
RAD. 1 ERC (0.97)
RAD. 2 ERC (0.97)

TRUE POSITIVE
FALSE POSITIVE

BA = BODY ARRAY COIL
ER = ENDORECTAL COIL

HEIJMINK, RADIOLOGY 244:184, 2007
3T MRI STAGING ACCURACY (vs. RPE SPECIMEN)

TRUE POSITIVE

FALSE POSITIVE

46 PATS.

EXPERIENCE ~ 3 MONTHS

RAD. 3 BAC (0.74)
RAD. 4 BAC (0.55)
RAD. 3 ERC (0.69)
RAD. 4 ERC (0.79)

BA = BODY ARRAY COIL
ER = ENDORECTAL COIL

HEIJMINK, RADIOLOGY 244:184, 2007
TEMPLATE GUIDED PERINEAL BIOPSY WITH 5-mm SAMPLING FRAME (TO DEFINE 0.5cc CANCER FOCI WITH 90% CERTAINTY)
MORE EXTENSIVE Bx IDENTIFIES MORE AND SMALLER CA, BUT CAN NOT RELIABLY MAP INDEX CA
- MORE EXTENSIVE Bx IDENTIFIES MORE AND SMALLER CA, BUT CAN NOT RELIABLY MAP INDEX CA

- ENDORECTAL MRI / DYN. MRI RELIABLY IDENTIFIES CA > 1cm³, AND WITH REFINEMENT (MRSI) SOME > 0.5cm³
MORE EXTENSIVE Bx IDENTIFIES MORE AND SMALLER CA, BUT CAN NOT RELIABLY MAP INDEX CA

ENDORECTAL MRI / DYN. MRI RELIABLY IDENTIFIES CA > 1cm³, AND WITH REFINEMENT (MRSI) SOME > 0.5cm³

TEMPLATE GUIDED STEREOTACTIC Bx FOR 3D - LOCALISATION OF INDEX TU.WITHIN PROSTATE IMPROVES TARGETED ABLATION
PREREQUISITES FOR SUCCESSFUL FOCAL THERAPY OF PROSTATE CA

- LOCALIZED, UNIFOCAL CANCER OF CLINICAL SIGNIFICANCE
- LESION CAN BE LOCALIZED WITH CLINICAL MEANS
- LESION CAN BE ABLATED AT LOW MORBIDITY
RADIOTHERAPY
CRYOTHERAPY
RADIOFREQUENCY
THERMAL LASER
VT PHOTODYNAMIC
FOCUSED ULTRASOUND
INJECTABLES
etc…
HIGH INTENSITY FOCUSED US (HIFU)

20-40 W/cm²

1600-2000 W/cm²

FREY, LANGENB. ARCH. KLEIN. CHIR. 264:253, 1950
LOCHMANN, ibid 264:235, 1950
SONABLATE™, FOCUS SURGERY

TRANSRECTAL HIFU
VARIABILITY OF LESION SIZE OBTAINED

1680W/cm, 8 RPE SPECIMENS

NO IMPACT OF SLANTING OR PCa vs. PBH

MADERSBACHER CANCER RES. 55:3346, 1995
"FOCAL"  HIFU OF LOW RISK PCa

1. F 3.5 cm 1680 W / cm²
2. F 3.5 cm 1680 W / cm²
3. F 3.5 cm 1680 W / cm²

Ca (BIOPSY pos.)

URETHRA

56mm

40mm

RECTUM

BIOPSIES

TRUS Bx

MADERSBACHER, CANCER RES. 55:3346, 1995
"FOCAL" HIFU → RP

10 PATIENTS (T1C, 1 CORE GL SC ≤ 6)

- CA. ALWAYS CORRECTLY TARGETED
- IN 3 PATS. COMPLETE TU. ABLATION
- IN 7 PATS. PARTIAL ABLATION (MEAN 53%, RANGE 38-77%)

MADERSBACHER, CANCER RES. 55:3346, 1995
"FOCAL" HIFU → RP

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- IN 7 PATS. PARTIAL ABLATION (MEAN 53%, RANGE 38-77%)

KEY PROBLEM: IDENTIFYING TUMOR

MADERSBACHER, CANCER RES. 55:3346, 1995
TRUS BIOPSY

6 – 18 MONTHS LATER:

NO TUMOR IN TREATED LOBE

RESIDUAL TUMOR = FAILURE
**MORBIDITY - "FOCAL" HIFU**

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANESTHESIA (mean)</td>
<td>67 mins</td>
</tr>
<tr>
<td>POSTOP. RETENTION</td>
<td>1/12</td>
</tr>
<tr>
<td>OTHER COMPLICATION</td>
<td>-</td>
</tr>
<tr>
<td>POTENCY MAINTAINED</td>
<td>6/7</td>
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</tbody>
</table>

**MORBIDITY OF "FOCAL" HIFU MINIMAL**

DEPT.UROLOGY, UNIVERSITY OF VIENNA
MULITMODALITY MRI MAKES A DIFFERENCE:

**HIFU HEMIABLATION IN UNILATERAL LOW RISK PCa IN 20 PATIENTS**

<table>
<thead>
<tr>
<th>BIOPSY STATUS* AT 6 MONTHS:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ANY CANCER</td>
<td>2 / 19 PATS.</td>
</tr>
<tr>
<td>“CLIN. SIGN.“ PCA</td>
<td>0 / 19 PATS.</td>
</tr>
</tbody>
</table>

* SAMPLING DENSITY > 1 CORE PER mL TISSUE, TREATED LOBE ONLY
<table>
<thead>
<tr>
<th></th>
<th>AFTER HIFU 3MONTHS</th>
<th>HEMIABL. 6MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERECTION</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>PAD FREE URINARY</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>CONTINENCE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECTAL TOXICITY</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>WET EJACULATION</td>
<td>60%</td>
<td>55%</td>
</tr>
</tbody>
</table>

EMBERTON J. UROL. E.publ. 1/21/2011
TARGETED ABLATION OF TU. BEARING PROSTATE SECTORS FEASIBLE AT LOW MORBIDITY
TARGETED ABLATION OF TU. BEARING PROSTATE SECTORS FEASIBLE AT LOW MORBIDITY

PROCEDURES REPEATABLE, NO BRIDGES BURNED
PREREQUISITES FOR SUCCESSFUL FOCAL THERAPY OF PROSTATE CA

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ASCERTAINEMENT OF ABLATION BY CE ULTRASONOGRAPHY

END OF ABLATION
ASCERTAINEMENT OF ABLATION BY CE ULTRASONOGRAPHY AND SEQUENTIAL MRI

END OF ABLATION

7d POST ABLATION

NO ENHANCEMENT / NECROSIS (HE) = 1.4 / 1
POTENTIAL HIFU TISSUE EFFECTS IN VIVO

- **THERMAL** BY ABSORPTION OF US ENERGY AND CONVERSION TO HEAT

- **BOILING** FROM HEAT ACCUMULATION

- **CAVITATION** BY BUBBLE FORMATION AND IMPLOSION

CHAPELON, CANCER RES. 52:6353, 1992
PAPREL, BJU INT. 95.881, 2005
PULSED CAVITATIONAL ULTRASOUND ("HISTOTRIPSY FRACTIONATION")
CAVITATION THRESHOLD

Intensity (SPTA W/cm²)

Frequency (Hz)

Degassed Water

CAVITATION

HEAT

GREY SCALE CHANGES DURING HIFU ("BUBBLES")

GRADE 1

GRADE 2

GRADE 3

UCHIDA, BJU INT 97:56, 2006
PSA AFTER "TOTAL" TRANSRECTAL HIFU ABLATION OF THE PROSTATE

ng/ml

m+SD

Baseline 3 6 9 12 18 24 30 36

Visual mode ≤ PSA 10 (n=27 Pats.)
Algorithm, ≤ PSA 10 (n=19 Pats.)
DUAL MODALITY PROBE PERMITS CONTINUOUS RF DATA ACQUISITION DURING TRANSRECTAL HIFU TREATMENT

SONABLATE-500™, FOCUS SURGERY, US
PULSE-ECHO ULTRASOUND DATA FROM IN-VIVO EXPERIMENTS

HIFU-INDUCES CHANGES VISIBLE IN THE B-MODE IMAGES.
TISSUE CHANGE MONITORING (TCM) BY SPECTRAL ANALYSIS OF BACKSCATTERED US

SONOBLATE 500 TCM™, US HIFU

MARBERGER, WCE CHICAGO 2010
VALIDATION OF TCM WITH REAL TIME THERMOMETRY DURING HIFU IN 5 PATIENTS

83% ORANGE ( > 75°C)
17% YELLOW (60-75°C)

MARBERGER, WCE CHICAGO 2010
VALIDATION OF TCM WITH REAL TIME THERMOMETRY DURING HIFU IN 5 PATIENTS

83% ORANGE (> 75°C)
17% YELLOW (60-75°C)

YELLOW ZONE: ABLATION UNRELIABLE, NEEDS RETREATMENT

MARBERGER, WCE CHICAGO 2010
• **DIRECTIONAL US BEAMS** - Deliver energy to targeted angular sectors
• **MULTIPLE ELEMENTS** - Control energy deposition along device
• **MULTI-FREQUENCY TRANSDUCERS** - Along with power, enable control over radial penetration

**TRANSURETHRAL MRI-GUIDED CONFORMAL US ABLATION**

CHOPRA, MED. PHYS. 35:1346, 2008
5 PATIENTS WITH LOCALIZED PCa: MRI GUIDED TRANSURETHRAL US ABLATION → RADICAL PROSTATECTOMY

Histopathology

100% kill
Target line

AVG. SPATIAL PRECISION 1-2 mm!

PROTOTYPE, PROFOUND™

SIDDIQUI, UROLOGY; 76:1506, 2010
HIFU ABLATION CAN BE MONITORED REAL-TIME BY
- US TISSUE CHANGE MONITORING
- MRI THERMOMETRY

INSUFFICIENT ABLATION CAN THEN BE REPEATED IMMEDIATELY FOR COMPLETE ABLATION
FOCAL THERAPY OF PROSTATE CANCER: WILL IT EVER WORK IN DAILY CLINICAL PRACTICE?
FOCAL THERAPY OF PROSTATE CANCER: WILL IT EVER WORK...

IN DAILY CLINICAL PRACTICE?
72 YRS., PSA 5.1 ng/ml, MRI CORRESPONDING 1/12 CORES 30% GL.SC. 3+3

SEX. ACTIVE
72 YRS., PSA 3.1 ng/ml, 6 MONTHS AFTER FOCAL HIFU

SEX. ACTIVE
75 YRS., PSA 3.8 ng/ml,
40 MONTHS AFTER FOCAL HIFU

SEX. ACTIVE
75 YRS., PSA 3.8 ng/ml,
40 MONTHS AFTER FOCAL HIFU

SEX. ACTIVE
PREREQUISITES FOR SUCCESSFUL FOCAL THERAPY OF PROSTATE CA

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THE SOBERING CONCLUSIONS...

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THE SOBERING CONCLUSIONS…

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BUT IS CANCER REALLY CURED?
Focal Treatment or Observation of Prostate Cancer: Pretreatment Accuracy of Transrectal Ultrasound Biopsy and T2-weighted MRI


OBJECTIVES

To test the hypothesis that men with prostate cancer (PCA) and preoperative disease features considered favorable for focal treatment would be accurately characterized with transrectal ultrasound (TRUS) guided focal therapy in a pre-treatment (MRI) biopsy format, we conducted a study of men with prostate cancers (grade 4/5, 1 involved core, <2 mm, PSA density ≤0.10, clinical stage ≤T2a) who were included in the study. Indolent RP pathology was defined as no Gleason 4/5, organ confined, tumor volume <0.5 mL, and focal treatment. According to these data, endorectal MRI is not sufficient to localize small tumors for focal treatment. UROLOGY 75: 472-477, 2010. © 2010 Elsevier Inc.

CONCLUSIONS

Transrectal biopsy identified men with indolent tumors favorable for focal treatment in 50% of cases. MRI findings of extracapsular extension and extensive tumor involving more than half of the gland are associated with unfavorable features, and may be useful in excluding patients from focal treatment. According to these data, endorectal MRI is not sufficient to localize small tumors for focal treatment. UROLOGY 75: 472-477, 2010. © 2010 Elsevier Inc.
Copy Number Analysis Indicates Monoclonal Origin of Lethal Metastatic Prostate Cancer


1Center for Cancer Genomics, Wake Forest University School of Medicine, Winston-Salem, NC, USA 2Laboratory of Cancer Genetics, Institute of Medical Technology, University of Tampere and Tampere University Hospital, Tampere, Finland 3Laboratory of Bioinformatics, Institute of Medical Technology, University of Tampere and Tampere University Hospital, Tampere, Finland 4PELICAN Laboratory, Departments of Pathology, Genetic Medicine, Health Sciences Informatics, Johns Hopkins University School of Medicine, Baltimore, MD, USA 5Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD, USA 6Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA 7Department of Oncology Biostatistics, Johns Hopkins University School of Medicine, Baltimore, MD, USA 8Computational Bioinformatics and Bio-imaging Laboratory, Department of Electrical and Computer Engineering, Virginia Polytechnic Institute and State University, Arlington, VA, USA
ACTIVE SURVEILLANCE IS PROBABLY EQUALLY EFFECTIVE

3.7 * 5.2 * 5.3 * 8.7 * 9.6 *

* 5/452 PATIENTS, ALL PSADT ≤ 1.6 YEARS

10-YRS. PCa-SPECIFIC SURVIVAL 97%

KLOTZ, J CLIN ONCOL, 26:126, 2010