Targeted/ Focal Therapy of Prostate cancer-
Pro. debate

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Targeted/Focal Therapy of Prostate cancer

- Rational
- Disease characteristics
- Imaging / Technologies
- Treatment options
- The Future
Targeted/Focal Therapy of Prostate cancer

Rational

- Is cure possible when it is necessary and is cure necessary when it is possible?”
  
  [Dr. Whitmore, Urology Chairman MSKCC, died of prostate cancer]

- “One wonders how much longer the era of radical therapy for small, early prostate cancers can last”.
  
  [Dr. P. Scardino, Urology Chairman MSKCC]

- “By the same reason that women have a mamography and are now spared from mastectomy by lumpectomy, - Men should have their “manography” and be offered prostate “lumpectomy” instead of a radical treatment” – AdMedTech org. official
Focal therapy might be almost as effective as radical (whole gland) treatment with similar low adverse effects as seen in those with active surveillance.

A significant proportion of men with organ confined, low-to-moderate risk prostate cancer may be spared from disease progression and have a high probability of preserving genitourinary and bowel function with focal therapy.

[Take home message- Focal P.ca. therapy workshop, Duke U. ; Feb. 2008]
Targeted/Focal Therapy of Prostate cancer

Disease Characteristics:

- **Unifocality** - In RP path., the proportion of unifocal tumors is 10% to 40% depending on patient selection, pathological sectioning technique and more.

- **Unilaterality** - 10-50%. (A rational for hemiablation?)

- Stage migration- Occurred over the last 2 decades (PSA era) for P.ca cancer. **Stamey** observed a decrease in patient age (from 64 to 59 years), mean serum PSA (from 25 to 8 ng/ml) and mean volume of the largest (index) cancer (5.3 to 2.4 cc). Similar trends were also found in the last decade only (The post PSA era) (**Adolfsson**).

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**A**, Prostate cancer with 4 tumor foci in 59y old man with PSA 4.3 ng/ml, clinical stage T1c and Gleason 6 in 2 right biopsy cores of a total of 8. **Volume of index lesion was 0.55 cc** and aggregate volume of secondary tumors was **0.25 cc**.

**B**, Low volume cancer in a 57y old man with PSA 3.8 ng/ml, clinical stage T1c, Gleason 6 in 1 of 8 biopsy cores and **total tumor volume 0.21 cc**.
Disease Characteristics (Cont.):

**Clinically significant tumor-**
- 0.5 cc is considered to be the size above which prostate cancer foci within the prostate are clinically significant. (Epstein, JHU.)

**Index tumor-**
- When examining 1,832 RP prostates by a whole mount technique, Ohori et al found that the mean volume of the 5 largest cancers in an individual was 2.13, 0.39, 0.17, 0.09 and 0.04 cm$^3$, respectively.
- In patients with multifocal disease, 80% of total tumor volume arose from the index tumor.
- When ECE (extracapsular extension) was found (28% of the above), 92% of it arose from the index tumor.
Disease Characteristics (Cont.):

- Over 80% of the non-index tumors are of <0.5cc and < Gleason grade 6 ..., therefore probably not significant (Bostwick, Bostwick labs.)

- Currently most patients undergoing treatment for localized disease are of low risk, (D’Amico’s criteria: <T1c/T2a, biopsy Gleason≤ 6, PSA < 10 ng/ml), of this population 28% have a single/unifocal tumor, and only 1% had extracapsular extension at the site of a secondary tumor. (D’Amico, Harvard MS)
Disease Characteristics (Cont.):

- Hall et al found that pathologic evaluation of the index tumor accurately predicted the clinical behavior of the entire gland regardless of synchronous tumors in > 90% of patients.
- Villers et al showed that 80% of secondary tumors are < 0.5 cc, a common criterion for depiction of clinical insignificance.
- Rukstalis et al found that the median ancillary lesion size was only 0.3 cc and concluded that 79% of men would likely have significant cancer eradicated if the index cancer was targeted.
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Imaging / Technologies

(....How do you find a focal disease ?)

- Imaging:
  - MRI – erMRI; stronger magnets(>1.5T);
  - Spectroscopy (MRSI); contrast enhancement;
  - Diffusion weighted;
  - TRUS- Hystoscan; Contrast enhancement;
  - Colored doppler; Elastography
  - PET-CT; PET-MRI
  - Molecular imaging ( J591-ecPSMA, etc....)

- Image registration & fusion
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Imaging / Technologies
(.....How do you find a focal disease ?)

- 3D prostate mapping
  - Biopsy-
    - Computer aided
      - TargetScan
      - Artemis
    - Saturated
  - “Intelligent probe” (Microcantilever for PSA)
MRI imaging

• Allows assessment of local/ regional extent of disease.
• Demonstrates the zonal prostate anatomy with excellent soft tissue resolution

“MR imaging and MR spectroscopic imaging are rapidly evolving as the most sensitive tool for noninvasive, anatomic, and metabolic evaluation of prostate cancer” (Hricak, Radiol. Clin. N. Am. 2007)
• Magnet strength of >1.5 T is required for high-quality MR and MRSI prostate imaging.
• Endorectal coil (er MRI) with a pelvic phased-array coil markedly improves image quality.
• T1-weighted axial images of the entire pelvis are obtained for the detection of nodal disease.
• T2-weighted images in 3 planes are used for tumor detection, localization, and staging.
• Spectroscopy (MRSI) improves,-
  a) P. ca. detection and localization.
  b) Provides metabolic information correlating with pathologic Gleason grade.
• The use of a dynamic contrast-enhanced MR sequence is optional and may aid cancer detection.
• Currently, 3D MRSI mapping of the entire prostate has resolution of 0.24 mL or smaller, depending on the parameters used.
• The setup for spectroscopic imaging is the same as for morphologic imaging.

The Kurhanewicz MRSI (per voxel) classification:
2. Normal,
3. Suspicious for cancer, (if \(\text{Cho}+\text{Cr})/\text{Cit} > 2\) SD above the normal PZ ratio)
4. Very suspicious for cancer. (if \(\text{Cho}+\text{Cr})/\text{Cit} > 3\) SD
| Author             | Sens   | Spec  | PPV   | NPV   | Accuracy          | Remarks                                                        |
|--------------------|--------|-------|-------|-------|-------------------|                                                               |
| 1 Shukla-Dave A    |        |       |       |       | 0.8-0.85 (AUC)    | Model for prediction of insignif. Ca. on RRP.                 |
| 2 Singh            |        |       |       |       | of 11 8          | TRUS Bx after MRI fusion                                       |
| 3 Wetter A         | 75%    | 87%   | 60%   | 93%   | 84%               | -MRI, -MRI+MRSI                                                |
| 4 Futterer JJ      | 69%    | 97%   |       |       | 87%               |                                                               |
| 5 Futterer JJ      | 88%    | 96%   |       |       | 94%               | 3T erMRI                                                       |
| 6 Amsellem-Ouaz D  | 73%    | 96%   | 92%   | 87%   | 88%               |                                                               |
| 7 Kumar V          | 100%   | 54%   |       | 100%  | 60%               | When 2-3 cores were taken from MRI +ve sites – sens= 100%      |
| 9 Heijmink SW      | 73-80% | 97-10 |       |       |                   |                                                               |
| 10 Zakian KL       | 56 (44-89 %) |       |       |       | 0.67 0.84        | Sens., Volume, Gleason grade correlated with Chol/Cit ratio   |
| 11 Akin O          |        |       |       |       | 0.67 0.84        | Accuracy correlates with tumor size for vol< 0.77 ml for vol> 0.77 ml |
However, despite encouraging data, currently (2008) MRI has not yet come of age as a single tool for driving Focal Treatment.

- Detection accuracy is sub-optimal.
  - ...still it may suffice for “smarter” biopsies.
- Lack of concrete data (designated trials).
- Wide range of reported results regarding detection
  - Operator dependent
  - Technology dependent
  - Evolving technology

Procedure definition......
- TRUS guided Bx following MRI “mapping”
- MRI guided
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- TRUS guided Bx following MRI mapping
  - “Per report” targeting (i.e. Rt. Apex)
  - Image alignment/ Fusion
    - Artemis
    - Traxtal

- MRI guided Bx
  - Robotic Bx gun (JHU)
  - Others
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Treatment modalities for Focal ablation

- Many –
  - Cryo,
  - HIFU,
  - PDT(TOOKAD),
  - focal Brachy,
  - IMRT
  - ……. 
  - Alcohol ?

- How to choose the right modality !?
  - Inconsequential ?
  - Costs ? Non-RCT small trials ? PR/ sexiness?
## Treatment modalities for Focal ablation

<table>
<thead>
<tr>
<th></th>
<th>HIFU</th>
<th>Cryotherapy</th>
<th>Radiation therapy</th>
<th>PDT</th>
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<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Thermal induced protein denaturation +</td>
<td>Disruption of cellular membrane +</td>
<td>DNA damage, cell damage + apoptosis</td>
<td>Light activated, oxygen dependent effects</td>
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<tr>
<td></td>
<td>coagulative necrosis + delayed vascular</td>
<td>delayed vascular occlusion</td>
<td>XRT, brachytherapy (removable or permanent</td>
<td>Transperineal light fibers</td>
</tr>
<tr>
<td><strong>Application</strong></td>
<td>Transrectal with cooling device</td>
<td>Transperineal</td>
<td>seed implants)</td>
<td></td>
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<tr>
<td><strong>Available systems</strong></td>
<td>Ablatherm, Sonablate 500</td>
<td>AccuProbe®, SeedNet™, Cryocare®</td>
<td>Numerous</td>
<td>Toookad in phase I/II trials for vascular</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>targeted phototherapy</td>
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<tr>
<td><strong>Retreatment</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Depends on dose delivered to surrounding</td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>normal tissues</td>
<td></td>
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<tr>
<td><strong>Limitations</strong></td>
<td>Treating anterior tumors + small prostates</td>
<td>Treating large prostates</td>
<td>XRT (prostate motion + proximity of bowel</td>
<td>Unknown</td>
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<td></td>
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<td>to target region), brachytherapy (large</td>
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<td>prostates + pts with significant urinary</td>
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<td></td>
<td></td>
<td></td>
<td>symptoms)</td>
<td></td>
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<tr>
<td><strong>Anesthesia</strong></td>
<td>General or regional</td>
<td>General or regional</td>
<td>XRT (none), brachytherapy or HDR (general</td>
<td>General or regional</td>
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<td></td>
<td></td>
<td></td>
<td>or regional)</td>
<td></td>
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<tr>
<td><strong>Treatment monitoring</strong></td>
<td>MRI or ultrasound</td>
<td>Ultrasound + thermosensors</td>
<td>CT, ultrasound, fluoroscopy, cystoscopy</td>
<td>MRI or ultrasound</td>
</tr>
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The Future -

- Focal therapy may within the next years fill the treatment gap between active surveillance/WW and radical therapies.
- Prostate cancer may become a chronic disease of the elderly.
- True “targeted” P.Ca. therapies are continuously investigated at the molecular /genetic /immune /nano-tech levels and may replace the “surgical” focal therapy within 10-20 years.
I think we should invest in this PSA company.