NON-GLEASON ASPECTS OF ACTIVE SURVEILLANCE

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New Haven, CT
Active surveillance is a management strategy designed to reduce treatment of patients with low-risk prostate cancer.
RATIONALE FOR ACTIVE SURVEILLANCE FOR LOW-RISK PROSTATE CANCER

- Reduce the risk of overtreatment (due to overdiagnosis) of clinically insignificant prostate cancer while retaining the option of definitive therapy for patients who are reclassified over time as high-risk
OVERDIAGNOSIS OF PROSTATE CANCER

- Overdiagnosis: Many clinically diagnosed prostate cancers will not progress or cause harm to the patient.
- Magnitude: 15% to 84% of all newly diagnosed prostate cancer cases
- The number of clinically diagnosed prostate cancers far exceeds the number of lethal cases
- Due in part to screening efforts
Estimated New Cancer Cases* in the US in 2015

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>26%</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>21%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.
Estimated Cancer Deaths in the US in 2015

<table>
<thead>
<tr>
<th>Cause</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>312,150</td>
<td>277,280</td>
</tr>
<tr>
<td>Prostate</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>23%</td>
</tr>
</tbody>
</table>
THE CHANGING FACE OF PROSTATE CANCER

• From a symptomatic, palpable, non-surgical disease that often presented at advanced stage in the first half of the last century
METASTATIC PROSTATIC CARCINOMA, WITH PATHOLOGIC FRACTURE

OSTEOBLASTIC BONY METASTASIS
THE CHANGING FACE OF PROSTATE CANCER

- To a disease that is now often asymptomatic, non-palpable, and organ-confined where initial patient management options include radical prostatectomy, radiation therapy, and active surveillance.
MINIMAL ADENOCARCINOMA
MINUTE PROSTATIC CARCINOMAS DETECTED BY PSA TESTING

RADICAL PROSTATECTOMY SECTION
OVERTREATMENT

- A common consequence of overdiagnosis
- In the United States most men diagnosed with low-risk prostate cancer still undergo primary curative therapy
- Many men may be subjected to side effects of therapy
IT IS ALL ABOUT RISK
STRATIFICATION AFTER BIOPSY
DIAGNOSIS OF PROSTATE CANCER

- Historically based on clinical and pathological parameters used to define clinically insignificant prostate cancer.

- In whole prostate glands:
  - Gleason score $\leq 6$
  - Organ-confined
  - Tumor volume $\leq 0.5$ cc (but recent proposal for $1.3$ cc)
EPSTEIN CRITERIA FOR ACTIVE SURVEILLANCE

- Prediction of small volume (< 0.5 cc), low-grade (Gleason score ≤ 6), and organ-confined cancer (correlated with outcome after surgery)
- Epstein JI et al. JAMA 271: 368, 1994

- Gleason score ≤ 6 in needle biopsy
- PSA density < 0.15
- < 3 cores positive
- No single core with > 50% involvement
EXPANDED CRITERIA FOR ACTIVE SURVEILLANCE

- The risk of significant tumors in men with clinical stage T2 lesions, 3 or fewer positive biopsy cores and less than 60% core involvement was comparable to that of men who met all active surveillance criteria (J Urol 190: 2033, 2013)

- ? Enroll patients with $3 + 4 = 7$ (especially if %4 is less than 5% or 10%)
MOST PATIENTS ELIGIBLE FOR ACTIVE SURVEILLANCE ARE VERY LOW RISK OR LOW RISK
2015 NCCN LOW RISK GROUPS

**VERY LOW RISK**
- cT1c (non-palpable)
- Gleason score $\leq 6$
- Serum PSA $< 10$ ng/ml
- Fewer than 3 prostate biopsy cores positive, less than or equal to 50% cancer in each core

**LOW RISK**
- cT1 to cT2a
- Gleason score $\leq 6$
- PSA $< 10$ ng/ml
INTERMEDIATE RISK ALLOWED IN SOME COHORTS

- cT2b – cT2c
- Gleason score of 7
  (usually 3+4=7)
- PSA 10 - 20 ng/ml
The Critical Role of the Pathologist in Determining Eligibility for Active Surveillance as a Management Option in Patients With Prostate Cancer: Consensus Statement With Recommendations Supported by the College of American Pathologists, International Society of Urological Pathology, Association of Directors of Anatomic and Surgical Pathology, the New Zealand Society of Pathologists, and the Prostate Cancer Foundation

Mahul B. Amin, MD; Daniel W. Lin, MD; John L. Gore, MD, MS; John R. Srigley, MD, FRCPA, FRCPa; Hema Samaratunga, MBBS, FRCPa; Lars Egevad, MD; Mark Rubin, MD; John Nacey, MD; H. Ballentine Carter, MD; Laurence Klotz, MD; Howard Sandler, MD; Anthony L. Zietman, MD; Stuart Holden, MD; Rodolfo Montironi, MD, FRCPa, IFCAP; Peter A. Humphrey, MD, PhD; Andrew J. Evans, MD; Jonathan I. Epstein, MD; Brett Delahunt, MD; Jesse K. McKenney, MD; Dan Berney, MD; Thomas M. Wheeler, MD; Arul M. Chinnaiyan, MD, PhD; Lawrence True, MD; Beatrice Knudsen, MD, PhD; M. Elizabeth H. Hammond, MD

*Arch Pathol Lab Med* 138 : 1390, 2014
## INCLUSION CRITERIA FOR ACTIVE SURVEILLANCE

<table>
<thead>
<tr>
<th>Study No. Patients</th>
<th>Clinical stage</th>
<th>PSA</th>
<th>Gleason score</th>
<th>Cancer extent</th>
<th>Other</th>
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<tr>
<td>Cooperberg and Glass 640</td>
<td>≤ T2</td>
<td>≤ 10</td>
<td>≤ 6</td>
<td>≤ 33% cores ≤ 50% any one core</td>
<td></td>
</tr>
<tr>
<td>Klotz et al 453</td>
<td></td>
<td>≤ 15</td>
<td>≤ 7 (3+4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selvadurai 471</td>
<td>≤ T2a</td>
<td>≤ 15</td>
<td>≤ 7 (3+4)</td>
<td>≤ 50% cores positive</td>
<td></td>
</tr>
<tr>
<td>Bul et al 2494</td>
<td>≤ T2</td>
<td>≤ 10</td>
<td>≤ 6</td>
<td>≤ 2 cores positive</td>
<td>PSAD ≤ 0.2</td>
</tr>
<tr>
<td>Patel et al 870</td>
<td>T1c</td>
<td>≤ 6</td>
<td></td>
<td>≤ 2 cores + ≤ 50% core any core</td>
<td>PSAD ≤ 0.15</td>
</tr>
</tbody>
</table>

Arch Pathol Lab Med 138 : 1390, 2014
QUANTITATION OF CANCER EXTENT IN PROSTATE NEEDLE CORE TISSUE

- Number of positive cores
- Fraction of positive cores
- Linear percentage of carcinoma in each positive core
- Total linear percentage of carcinoma in all cores
- Greatest percentage of linear carcinoma in a single core
- Linear millimeters of carcinoma in each positive core
- Total linear millimeters in all cores
- Greatest linear millimeters in a single core
Interrelatedness of Measures of Tumor Extent in Needle Biopsy

Correlation coefficients for measures of tumor extent

<table>
<thead>
<tr>
<th>Variable</th>
<th>Positive cores</th>
<th>Fraction</th>
<th>Length</th>
<th>GPC</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive cores</td>
<td>1</td>
<td>.93</td>
<td>.67</td>
<td>.51</td>
<td>.70</td>
</tr>
<tr>
<td>Fraction</td>
<td>.93</td>
<td>1</td>
<td>.63</td>
<td>.52</td>
<td>.69</td>
</tr>
<tr>
<td>Length</td>
<td>.67</td>
<td>.63</td>
<td>1</td>
<td>.70</td>
<td>.83</td>
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<tr>
<td>GPC</td>
<td>.51</td>
<td>.52</td>
<td>.70</td>
<td>1</td>
<td>.81</td>
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<tr>
<td>TPC</td>
<td>.70</td>
<td>.69</td>
<td>.83</td>
<td>.81</td>
<td>1</td>
</tr>
</tbody>
</table>

Positive cores, number of positive cores; Fraction, number of positive cores/total number of cores; Length, total tumor length in mm; GPC, greatest percentage of carcinoma in a single core; TPC, total percentage of carcinoma in all cores.

MOST COMMONLY USED NEEDLE CORE TUMOR EXTENT MEASURES FOR ACTIVE SURVEILLANCE ENROLLMENT

- **NCCN**: Number of positive cores and greatest percentage carcinoma in a single core (50% cutoff)

- *Consensus statement summary of 7 large active surveillance cohorts*:
  - Number of positive cores (3 of 7)
  - Greatest percentage of positive cores (3 of 7)
  - Fraction of positive cores (2 of 7)
ISSUES WITH QUANTITATION OF TUMOR EXTENT IN NEEDLE CORE TISSUE

- Measuring discontinuous foci of cancer
- Tissue core and tumor fragmentation
- Inadequate sectioning
- Inadequate core length
- Whether total core length should include extraprostatic tissue

Arch Pathol Lab Med 138 : 1390, 2014
What is the % surface area involvement?
What is the % surface area involvement?

J. Prostate Biopsy: Needle Core Biopsy, Left Middle M: Adenocarcinoma, Gleason score 7 (4+3). Involves approximately 95% of the core.

Courtesy Dr. David Grignon
DO DISCONTINUOUS FOCI IN NEEDLE CORE TISSUE REPRESENT SAMPLING OF ONE TUMOR?

- **Correlation with whole glands**: In 78% of patients a single tumor focus was present in the corresponding region of the whole gland (Arias-Stella JA, et al. AJSP, 2014 [Epub ahead of print])

- **Clonal evaluation by dual ERG/SPINK1 immunohistochemistry**: (Mod Pathol 27: 229A, 2014 [abstract]) : 22% of needle cores with discontinuous foci showed discordant ERG/SPINK1 status, consistent with multiclonal tumor.
MEASURING DISCONTINUOUS FOCI

- Few published studies
- Additional data with large number of patients with clinical follow-up needed
- Consensus statement recommendation for reporting:

  Adenocarcinoma, Gleason grade 3 + 3 = score of 6, involving 1 of 6 cores, with 2 discontinuous foci measuring 2 mm in aggregate, involving 10% of one core, and spanning 70% of the core.
CORE FRAGMENTATION

- With fragmentation of more than one core in a container it may not be possible to provide number of positive cores and fraction of cores positive.
- Consensus paper then recommends reporting extent for entire specimen.

INADEQUATE SECTIONING

- Single needle core (top right) is more readily embedded in a flat plane compared to multiple cores (bottom right) and especially core fragments.
- One core per cassette optimal.
- Consensus paper recommends no more than 2 cores per cassette.

Arch Pathol Lab Med 138:1387, 2014
PROSTATE NEEDLE CORE LENGTH

- Most needle cores = 15 mm in length
- 50% involvement = 7.5 mm
- But for 6 mm core 50% = 3 mm
- Significance not clear
- Consensus paper recommendation:

  *If core length is less than 6 mm, report core length.*
SHOULD CORE LENGTH INCLUDE NON-PROSTATIC TISSUE

- Consensus paper recommendation: No
EXCLUSION FROM ACTIVE SURVEILLANCE

- Ductal adenocarcinoma
- Non-glandular carcinomas such as sarcomatoid, squamous, or small cell carcinoma
EXCLUSION FROM ACTIVE SURVEILLANCE

- Extraprostatic extension or lymphvascular invasion in needle biopsy (proposed in Arch Pathol Lab Med 138, 1390, 2014)
- Not formally tested
PERINEURAL INVASION ON NEEDLE BIOPSY IS NOT AN EXCLUSION CRITERION

2 of 3 studies supportive:
J Urol 186:470, 2011;
Urology 84:149, 2014
FOCAL GLANDULAR ATYPIA (ATYPICAL SMALL ACINAR PROLIFERATION)

- Foci of atypia only need be investigated in cancer cases when work-up with immunostains would change management from active surveillance to treatment.

- Example: Change from 2 cores to 3 cores positive
BIOPSY APPROACHES PRIOR TO ENROLLMENT IN ACTIVE SURVEILLANCE

- Some physicians require extended biopsy sampling prior to enrollment in active surveillance
- At Yale Urology, MRI-ultrasound fusion sampling required, with around 25 needle cores submitted
- Rationale: Rule out or rule in high-grade disease
SURVEILLANCE SCHEDULES

- Variable
- Most utilize serial PSA, digital rectal examination, and repeat prostate biopsies
- Frequency of evaluation variable: Every year a common target
DEFINITION OF “PROGRESSION” OR RECLASSIFICATION ON ACTIVE SURVEILLANCE: NEEDLE BIOPSY FINDINGS

- Gleason score $> 6$
- Primary Gleason grade $\geq 4$
- $>33\%$ to $>50\%$ positive cores
- 3 or more cores positive
- $>50\%$ involvement of any single core

Arch Pathol Lab Med 138:1387, 2014
# FREQUENCY OF “PROGRESSION” ON ACTIVE SURVEILLANCE

<table>
<thead>
<tr>
<th>Study No. Patients</th>
<th>Median follow-up (months)</th>
<th>Grade Progression(%)</th>
<th>Treated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooperberg and Glass 640</td>
<td>47</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>Klotz et al 453</td>
<td>82</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Selvadurai 471</td>
<td>68</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Bul et al 2494</td>
<td>19</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

Arch Pathol Lab Med 138, 1390, 2014
## Reasons for Intervention on Active Surveillance

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of Patients</th>
<th>% of Treated Patients</th>
<th>% of Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short PSA doubling time</td>
<td>116</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>Grade progression</td>
<td>94</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Patient preference</td>
<td>16</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Stage progression</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Biopsy cancer extent increase</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

PATHOLOGICAL OUTCOMES AFTER ACTIVE SURVEILLANCE

- Intermediate endpoint since many years/decades of clinical follow-up needed for low-risk prostate cancer patients on active surveillance
- Radical prostatectomy findings in 7,486 candidates for active surveillance:
  - **Very low risk**: 13% upgrade; 9% non-organ confined
  - **Low risk**: 22% upgrade; 23% non-organ confined

*J Urol* 190: 1218, 2013
CANCER-SPECIFIC SURVIVAL IN ACTIVE SURVEILLANCE

- 993 patients favorable (79%) or intermediate risk (21%; PSA 10-20 and/or Gleason score 3+4)
- Median follow-up of 6.4 years
- 2.8% (28) developed metastasis at median of 7.3 years
- Of the 28, 44% had 3+4 =7 at diagnosis and had 3+4 =7 eventually
- 1.5% (15 patients) died of prostate cancer

CANCER-SPECIFIC SURVIVAL IN ACTIVE SURVEILLANCE

CUMULATIVE HAZARD RATIO OF NON-PROSTATE CANCER DEATH VS. PROSTATE CANCER DEATH

PREDICTION OF EARLY METASTASIS

- PSA doubling time of less than 3 years (is sensitive but not specific and is not recommended as a trigger for intervention)
- Gleason score 8 to 10

Gleason grade 4 + 4 = score of 8
MAJOR LIMITATION OF ACTIVE SURVEILLANCE

- A significant proportion have undetected high-grade prostate cancer
NEW TECHNIQUES TO DETECT AGGRESSIVE PROSTATE CANCER

- Multiparametric MRI
- MRI/ultrasound biopsy approach
- Serum and urine biomarkers
- Tissue biomarkers
Lesion suspicious for prostate cancer at yellow arrowheads

JAMA 313:391, 2015
USE OF MULTIPARAMETRIC MRI AND MRI/ULTRASOUND FUSION TO GUIDE BIOPSIES

JAMA Online Jan. 28, 2015
USE OF MULTIPARAMETRIC MRI AND MRI/ULTRASOUND FUSION TO GUIDE BIOPSIES

- Targeted biopsy detected 30% more high-risk (Gleason grade 4+3) cancers compared to standard 12 core biopsy, and 17% fewer low-risk cancers

MR AND MR/ULTRASOUND FUSION IN ACTIVE SURVEILLANCE

- Some require MR and fusion targeted biopsies before enrollment in active surveillance
- Could increase detection of higher-risk and decrease detection of lower-risk cancers
- MR: Use in follow-up in active surveillance to reduce number of biopsies. Supplant the need for biopsy?
SERUM MARKERS: PROSTATE SPECIFIC ANTIGEN

- Total PSA
- PSA density (Total PSA/gland volume)
- PSA velocity (rate of change of PSA over time)
- % free PSA
- [-2]proPSA
- Prostate Health Index (combination of total PSA, free PSA, and proPSA)
ADDITIONAL PROPOSED SERUM BIOMARKERS

- Limited number of circulating biomarkers have been evaluated in the active surveillance setting
- Serum microRNAs
- Primary circulating prostate cancer cells
- In one review % free PSA most useful

(Curr Opin Urol 24:293, 2014)
URINARY BIOMARKERS IN ACTIVE SURVEILLANCE

- Urinary prostate cancer antigen 3 (PCA3) and TMPRSS2:ERG fusion (right) have been correlated with adverse biopsy features.
- But not consistently associated with active surveillance outcomes, as an independent factor.


Endocr Rel Cancer 21:R143, 2014
“Men with clinically localized disease could consider use of a tumor-based molecular assay to stratify better risk of adverse pathology at radical prostatectomy or chance of biochemical recurrence or disease-specific mortality after radical prostatectomy.”
TISSUE BIOMARKERS AND ACTIVE SURVEILLANCE : RNA PROGNOSTIC SIGNATURES

- Example: Cell cycle progression (CCP) score: average RNA expression of 31 CCP genes
- May provide additional information beyond PSA, clinical stage and Gleason score
- In one study 32% of test results led to definitive or possible changes in treatment
- Added value with MR or MR/US fusion
- 7 published retrospective papers but no prospective evaluation in clinical trials
TISSUE BIOMARKERS AND ACTIVE SURVEILLANCE

- **Genomic Prostate Score**:
  Multigene (12 cancer-related genes) RT-PCR expression assay

- **ERG expression** *(Eur Urol – Epub ahead of print 2014)*

- **PTEN loss and upgrading** *(Mod Pathol 28:128, 2015)*

- **Exome genotyping using SNPs** *(Plos One 9:e104146, 2014)*

**ERG Expression**
BIOMARKERS IN URINE, SERUM, AND TISSUE IN ACTIVE SURVEILLANCE

- Refinement of current risk stratification strategies needed
- Issues:
  - Tumor heterogeneity and clinical sampling
  - Proof of added value beyond PSA, clinical stage, cancer extent, Gleason score, and now mMRI
  - Prospective validation in powered studies
  - Testing in clinical trials
CHALLENGES FOR ACTIVE SURVEILLANCE

- Management of patient anxiety for men considering or enrolled in active surveillance
- For physicians, excluding potentially life-threatening prostate cancer
- For the lay public, increased education and awareness of the “insignificant prostate cancer” concept

BJU Int 113:E13, 2014
FUTURE DIRECTIONS/NEEDS

- Prospective clinical trials
- Testing of new enrollment and reclassification criteria
- Ultimately: decrease need for active surveillance by decreasing diagnosis of potentially indolent prostate cancer. Examples: risk assessment tools and nomograms before biopsy and biomarkers for high-grade and lethal prostate cancer (to replace PSA-based screening).
FUTURE DIRECTIONS/NEEDS

- Standardization
- Incorporation of new radiological imaging technologies
- Incorporation of molecular biomarkers