Guidelines for Active Surveillance of Prostate Cancer

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Summary and Recommendations

1. There is no single set of recommendations for Active Surveillance of prostate cancer
2. There are recommendations for what constitutes low risk cancer - see ref by Bastian et al, Boccon-Gibod.
3. On this basis I suggest as criteria for low-risk cancer
   a. Stage T1c
   b. No Gleason pattern 4 or 5 (i.e. in effect Gleason 3+3)
   c. <3 positive cores
   d. <50% cancer involvement per core
   e. PSA ≤ 10ng/ml
4. On the basis of all the papers below (collectively) I suggest the following
   a. Inclusion Criteria for Active Surveillance for CA Prostate
      i. Stage T1c or T2 (Hardie et al, Soloway et al 2008, Van den Bergh 2009)
      ii. Gleason ≤ 6 (i.e. no pattern 4 or 5)
      iii. PSA ≤ 10ng/ml (Dall’Era, Van Den Bergh, Soloway 2010)
      iv. ≤ 2 cores positive with no core more than 50% involved (Whitson and Carroll)
   b. Follow up Protocol
      i. PSA every 3 months for 1 year then 6 monthly (see Bastian, Table 2 – there are various protocols)
      ii. DRE each time
      iii. TRUSB every 12 months (there is no consensus I can find about this but Whitson and Carroll 2010 say that at present surveillance biopsy is critical component of any Active Surveillance strategy, and that PSA kinetics are not sufficient to define disease progression and need for Rx, so it makes sense to biopsy often?)
   c. Indications for Active Rx (Soloway 2008)
      i. PSA doubling time < 3 years (see Van den Bergh 2009) – PSA DT to be assessed only after 1yr of follow up and using at least 5 PSA measurements (Van den Bergh 2009)
      ii. Re biopsy with Gleason ≥7
      iii. Increase in tumour volume – i.e. >2 cores positive, or any core >50% involvement
      iv. Stage progression - >T2
      v. Patient preference
Review of Literature

(Hardie et al. 2005)

PRIAS study

Table 1 – Inclusion criteria

1. Men should:
   - Have histologically proven adenocarcinoma of the prostate
   - Be fit for curative treatment
   - Be willing to attend the follow-up visits
   - Not have received former therapy for prostate cancer
2. Clinical stage is T1C or T2
3. Gleason score is ≤6 and ≤2 biopsy cores are invaded with prostate cancer
4. PSA is ≤10 ng/ml and PSA density is ≤0.2 ng/ml/ml

PSA = prostate-specific antigen.

PSA measurements every 3mths and Biannual clinical examination for first two years
Then biannual PSA and annual clinical examination thereafter
Repeat TRUSB at 1,4,7,10 yr
(Soloway et al 2008)

Gleason ≤6, Serum PSA ≤15, Stage ≤T2, low vol disease (<50% of two biopsy cores)

Serum PSA and DRE every 3mths for 2yrs and every 6mths thereafter
Repeat TRUSB focusing on periph zone 6-12mths after initial diagnosis then as indicated

Decision to continue AS based on
1. PSA DT – PSA DT for treatment group was >2years. Signif diff from AS group (p=0.05) – see refs
2. Rebiopsy with Gleason ≥7
3. Increase in tumour volume
4. Stage progression
5. Patient preference

See references to Klotz and D’Amico

(Dall’Era et al 2008)

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>Common Entry Criteria for Active Surveillance</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Gleason sum</td>
</tr>
<tr>
<td>PSA</td>
</tr>
<tr>
<td>% positive cores</td>
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<tr>
<td>% single core involvement</td>
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<tr>
<td>PSA kinetics</td>
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</table>

for psychosocial interventions and support. However, results from these trials are several years from being obtained. Although these data are pending, we here-with put forward our conservative recommendations given the current state of knowledge. Men should have a low (<10 ng/mL) and stable PSA level, a Gleason grade ≤6, clinical stage T1 to T2a disease, and low-volume disease as assessed by extended pattern (≥12 needle cores) biopsy. Men should be followed closely with frequent PSA measurements (every 3–4 months) with digital rectal examinations performed every 3 months to 6 months and imaging (if performed) every 9 months to 12 months (Table 3). Repeat prostate needle biopsy should be performed after 1 year of surveillance and then every 12 to 24 months or as indicated by changes in PSA or findings on digital rectal examination. Although a significant number of men may ultimately require other forms of therapy, active surveillance offers the opportunity to delay active treatment and its associated morbidities until evidence of clinical progression is found.
results of PRIAS study

Study of 500 patients with
PSA <10
T1c/T2
Gleason ≤6
One or two positive cores

Follow up
• PSA every 3mths and DRE every 6 months for first 2 yrs
• Then PSA every 6mths and DRE annually
• Repeat TRUSB at 1,4,7 yrs
• Active Rx IF
  o PSADT 0-3 yrs at any stage
  o Stage >T2
  o Or if biopsies show > two cores or Gleason >6
  o If PSADT 3-10 years at any stage then yearly TRUSB instead of above schedule
  o PSADT advised to be assessed only after 1yr of follow up and using 5 PSA measurements
  o PSA >20 requires bone scan

Results
• 25% of men stopped AS after 2 years of follow up
• see other results

Kattan Nomogram - ?useful
See http://www.usrf.org/news/WW_for_CaP/examples.html
A rapid pretreatment PSA rise is associated with an increased risk of dying from CAP.

**Definitions of insignificant or low risk CAP**

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Epstein et al [5] and Bastian et al [18] | Clinical stage T1c  
PSA density $<0.15$ ng/ml  
No Gleason pattern 4 or 5  
$<3$ positive cores  
$<50\%$ cancer per core |
| D’Amico et al [22]           | PSA level $\leq 10$ ng/ml  
No Gleason pattern 4 or 5  
Clinical stage T2a or lower |
| Dall’Era et al [13]          | PSA level $\leq 10$ ng/ml  
No Gleason pattern 4 or 5  
Clinical stage T2a or lower  
PSA density $<0.15$ ng/ml  
$<33\%$ positive cores |
| Patel et al [74]             | Clinical stage T3 or lower  
Gleason sum $\leq 7$ |
| Soloway et al [47]           | Clinical stage T2 or lower  
PSA level $<15$ ng/ml  
No Gleason pattern 4 or 5  
$<50\%$ cancer per two positive cores |
| Van den Bergh et al [72] (PRIAS) | Clinical stage T1c–T2b  
No Gleason pattern 4 or 5  
PSA density $<0.20$ ng/ml  
PSA level $<10$ ng/ml  
Fewer than three positive cores |
| Van As et al [38]            | Clinical stage T1–T2a  
Gleason sum $\leq 7$ (3 + 4)  
PSA level $<15$ ng/ml  
$<50\%$ of biopsy cores positive |
| Dall’Era et al [14] (commonly used criteria) | No Gleason pattern 4 or 5  
PSA level $<10$ ng/ml and stable PSA kinetics  
$\leq 50\%$ single core involvement  
$\leq 33\%$ positive cores |

PSA = prostate-specific antigen; PRIAS = Prostate Cancer Research International: Active Surveillance.
Table 2 – Follow-up criteria during active surveillance

<table>
<thead>
<tr>
<th>Study</th>
<th>DRE</th>
<th>PSA</th>
<th>TRUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van As et al [18]</td>
<td>Every 3 mo for 2 yr, then every 6 mo</td>
<td>Year 1: monthly, Year 2: every 3 mo, afterwards: every 6 mo</td>
<td>At 18-24 mo, then biannually, No mention</td>
</tr>
<tr>
<td>Dall’Era et al [46]</td>
<td>Every 3 mo</td>
<td>Every 3 mo</td>
<td>Every 12-24 mo</td>
</tr>
<tr>
<td>Carter et al [31, 40]</td>
<td>Every 3 mo</td>
<td>Every 6 mo</td>
<td>Yearly</td>
</tr>
<tr>
<td>Klotz et al [32]</td>
<td>Every 3 mo for 2 yr, then every 6 mo if PSA level is stable</td>
<td>Every 3 mo for 2 yr, then every 6 mo</td>
<td>At 12-18 mo</td>
</tr>
<tr>
<td>Padal et al [74]</td>
<td>Every 3 mo for 1 yr, then every 6 mo</td>
<td>Every 3 mo for 1 yr, then every 6 mo</td>
<td>At 6 mo</td>
</tr>
<tr>
<td>Sooseway et al [47]</td>
<td>Every 3 mo</td>
<td>Every 3 mo for 2 yr, then every 6 mo</td>
<td>At 6-12 mo, afterwards when indicated,</td>
</tr>
<tr>
<td>Hardie et al [43]</td>
<td>Every 3-6 mo for 2 yr, then every 6 mo</td>
<td>Every 3-6 mo for 2 yr, then every 6 mo if PSA is stable</td>
<td>Not routine, Optional</td>
</tr>
</tbody>
</table>

DRE = digital rectal examination; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

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Table 3 – Indications for active treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment criteria</th>
<th>Median age, yr (range)</th>
<th>Percentage of patients with active treatment, % (total no of patients)</th>
<th>Mortality (related to prostate cancer)</th>
<th>Median follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van As et al [18]</td>
<td>PSAV &gt;1 ng/ml per year or Gleason score ≥4 + 3 or &gt;50% cancer per core</td>
<td>67 (50-79)</td>
<td>20 (126)</td>
<td>None</td>
<td>22</td>
</tr>
<tr>
<td>Dall’Era et al [46]</td>
<td>Gleason score ≥7 on biopsy, rising PSA, increase in volume by biopsy parameters</td>
<td>68.4 (46-86)</td>
<td>21 (121)</td>
<td>None</td>
<td>24</td>
</tr>
<tr>
<td>Carter et al [31, 49]</td>
<td>Gleason score ≥7 or biopsy, any pattern 4, 5 &gt;2 cores involved, &gt;50% any single core involved PSA DT = 2 yr</td>
<td>65.7 (45.8-81.3)</td>
<td>31 (126)</td>
<td>None</td>
<td>23</td>
</tr>
<tr>
<td>Klotz et al [22]</td>
<td>Gleason score ≥8 or PSA DT = &lt;2 yr or Gleason score ≥7 (4 + 3)</td>
<td>NA</td>
<td>34 (259)</td>
<td>None</td>
<td>64</td>
</tr>
<tr>
<td>Patel et al [74]</td>
<td>Gleason score increase, PSAV = 0.75/gd, increases DRE/TRUS-detected lesion, increase biopsy volume</td>
<td>Mean: 65.3 (44-79)</td>
<td>35 (84)</td>
<td>None</td>
<td>44</td>
</tr>
<tr>
<td>Hardie et al [43]</td>
<td>Rising PSA, clinical judgment</td>
<td>70.5 (59-83)</td>
<td>14 (40)</td>
<td>None</td>
<td>42</td>
</tr>
<tr>
<td>Resenhofer et al [39]</td>
<td>Increase in tumour volume, Gleason score progression, urinary symptoms, change of DRE, patient preference</td>
<td>69.8 (59-71)</td>
<td>29 (178)</td>
<td>None</td>
<td>40</td>
</tr>
<tr>
<td>Sowday et al [47]</td>
<td>Gleason score increase, PSA and PSA DT increase, stage progression, increase biopsy volume, patient preference</td>
<td>67 (mean: 65.62)</td>
<td>&lt;1 (94)</td>
<td>None</td>
<td>45.5 (mean)</td>
</tr>
</tbody>
</table>

PSA = prostate specific antigen, PSA DT = PSA doubling time, PSAV = PSA velocity, DRE = digital rectal examination; TRUS = transrectal ultrasound. NA = not available.
4. Conclusions

In summary, active surveillance is an alternative treatment option to immediate treatment of men with presumed low-risk PCa. It seems that criteria used to identify men with low risk PCa are rather similar, and immediate treatment of men meeting these criteria may result in an unnecessary number of treatments in these highly selected patients. However, today the criteria to predict low-risk, organ-confined PCa are not perfect, and certain number of patients that warrant immediate treatment may be missed. Furthermore, information from randomised trials comparing active surveillance and active treatment will provide additional insight into the outcome of active surveillance compared to active treatment and the required follow-up strategies.

Hopefully, by using the modernised progression criteria, no patients with progression will miss the window of curability. With the improvement of molecular biomarkers, the identification of PCA progression may become easier and more accurate.

(Boccon-Gibod et al 2009)

Table 1 – Epstein criteria for very low-risk prostate cancer according to Barocas et al [8]

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>&lt;10 ng/ml</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>T1 or T2a</td>
</tr>
<tr>
<td>PSA density</td>
<td>&lt;0.15</td>
</tr>
<tr>
<td>Positive biopsy cores</td>
<td>&lt;1/3</td>
</tr>
<tr>
<td>Gleason score</td>
<td>≤ 6</td>
</tr>
</tbody>
</table>

PSA = prostate specific antigen.
Doesn’t offer any views about when to instigate Active Rx

Says probably not necessary to repeat saturation biopsies

*(Dall'era et al 2010)*

*What’s known on the subject? and What does the study add?*

The risks of delayed radical prostatectomy for men who progress on active surveillance are largely unknown. Two series have reported that prostatectomy after active surveillance has similar results to immediate therapy. Our data add to this growing body of evidence that appropriately selected men with prostate cancer can undergo active surveillance with delayed prostatectomy without added risk of missing an opportunity for cure as the majority of tumours remain organ confined.

*(Soloway et al 2010)*

- Data suggests that if guidelines for AS are narrowly defined to include only those patients with
  - Gleason 6
  - PSA<10
  - Tumour vol <20% in two or fewer cores
- a lower percentage of AS patients will likely require treatment when compared to other AS series
Retrospective cohort study that looked at PDADT and PSA velocity and surveillance biopsy results in men with low-risk cancer who chose AS as their initial management strategy
Inclusion and exclusion criteria
• T1C
• PSA Density < 0.15ng/ml/cm³
• Gleason ≤6
• ≤ 2 cores positive with no core more than 50% involved in at least a 12 core biopsy scheme
Authors suggest that at present surveillance biopsy is a critical component in any AS strategy and that PSA kinetics are not sufficient to define disease progression and need for Rx

Appears to fly in face of existing literature; In men undergoing Rad Prost higher PSA Velocity is associated with both worse Gleason score and T stage. In men undergoing either RP or RT a PSA velocity >2.0 ng/ml/year in the year before diagnosis predicts CAP specific mortality.
References used


• Dall'era, M.A., Cowan, J.E., Simko, J., Shinohara, K., Davies, B., Konety, B.R., Meng, M.V., Perez, N., Greene, K. & Carroll, P.R., 2010, Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment, BJU international.


• Whitson JM & Carroll PR, Active Surveillance for Early-Stage Prostate Cancer: Defining the triggers for intervention, Journal for Clinical Oncology, 28(17), pp. 2807-9.