Assessment of senior adults with advanced prostate cancer for chemotherapy: SIOG guidelines

Jean-Pierre Droz, MD, PhD
Professor of Medical Oncology
Claude-Bernard Lyon 1 University
Centre Léon-Bérard, Lyon, France


At diagnosis, 64% of men aged ≥ 65 years and 27% aged ≥ 75 years

Number of men aged 70+ and 80+ in US (1950 – 2050)

Baby boom generation: a LOT of prostate cancer!

Standard Prostate cancer treatment

- Localized
  - Prostatectomy
  - Radiation therapy
  - Brachytherapy / HIFU
- Advanced
  - Androgen deprivation
  - Chemotherapy
  - Palliative treatments

Life expectancy in senior adults: a large variability reflecting health status variability

A question of population

Chances of survival depends of health status

A question of individual

Vulnerable* and frail** senior adults are the majority and are at death risk!

*Vulnerable: need for assistance in ≥ 1 (or ≥ 2 if incontinence) activities of mobility or daily living or cognitive impairment without dementia or bowel + urinary incontinence
**Frail: need for assistance in ≥ 2 (or ≥ 3 if incontinence) activities of mobility or daily living or dementia or bowel + urinary incontinence

Walter LC et al. JAMA 2003, 289, 2750-2756

Rockwood K et al. Lancet 1999, 353, 205-206
Domains of expertise of health status in senior adults: Which have been our choices?

Comorbidity is a key predictor of life expectancy

1. Example of radical prostatectomy
2. Example of radio-HT therapy

### Charlson comorbidity index

<table>
<thead>
<tr>
<th>Assigned weight</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (each)</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease (except hemiplegia)</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>Connective tissue disease</td>
</tr>
<tr>
<td></td>
<td>Ulcer disease</td>
</tr>
<tr>
<td></td>
<td>Mild liver disease</td>
</tr>
<tr>
<td></td>
<td>Diabetes (without complications)</td>
</tr>
<tr>
<td>2 (each)</td>
<td>Hemiplegia</td>
</tr>
<tr>
<td></td>
<td>Moderate or severe renal disease</td>
</tr>
<tr>
<td></td>
<td>Diabetes with end-stage organ damage</td>
</tr>
<tr>
<td></td>
<td>2nd solid tumour (non metastatic)</td>
</tr>
<tr>
<td></td>
<td>Leukaemia</td>
</tr>
<tr>
<td></td>
<td>Lymphoma, multiple myeloma</td>
</tr>
<tr>
<td>3</td>
<td>Moderate or severe liver disease</td>
</tr>
<tr>
<td>6 (each)</td>
<td>2nd metastatic solid tumor, AIDS</td>
</tr>
</tbody>
</table>

**Total score: [0–30]**

Comorbidity is the strongest predictor of non prostate cancer mortality (multivariate analysis)

<table>
<thead>
<tr>
<th></th>
<th>All cause mortality</th>
<th>Prostate Cancer mortality</th>
<th>Non-prostate Cancer mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR p</td>
<td>RR p</td>
<td>RR p</td>
<td></td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>0.41 &lt;0.00</td>
<td>0.35 0.001</td>
<td>0.44 0.00</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>0.90 ns</td>
<td>0.41 0.001</td>
<td>1.10 0.04</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.94 &lt;0.00</td>
<td>1.04 0.14</td>
<td>1.05 0.04</td>
</tr>
<tr>
<td>Charlson 2+</td>
<td>2.32 &lt;0.00</td>
<td>1.43 0.23</td>
<td>3.03 &lt;0.00</td>
</tr>
<tr>
<td>Biopsy grade</td>
<td>1.28 0.005</td>
<td>2.08 &lt;0.001</td>
<td>1.15 0.15</td>
</tr>
<tr>
<td>baseline PSA</td>
<td>1.55 &lt;0.00</td>
<td>2.51 &lt;0.00</td>
<td>1.22 0.10</td>
</tr>
<tr>
<td>Income $10,000 (&gt; versus &lt;)</td>
<td>0.91 0.014</td>
<td>0.96 0.66</td>
<td>0.90 0.008</td>
</tr>
</tbody>
</table>

1,611 men with clinically localized prostate cancer and 45-70 age, race and comorbidity matched controls

### Radial prostatectomy complications:

**SEER-Medicare database**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No or minimal comorbidity*</th>
<th>Moderate or severe comorbidity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (%) of cancer</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>&lt;70</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>≥70</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Race</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Black</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>White</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Charlson comorbidity</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*The Romano–Charlson index is a weighted sum of 27 assigned conditions.

Romano–Charlson index is a strongly significant predictor of post-operative and late urinary complications

### No benefit of radiation therapy plus androgen deprivation if moderate/severe comorbidity

**Overall survival, %**

<table>
<thead>
<tr>
<th>Years after randomization</th>
<th>No or minimal comorbidity*</th>
<th>Moderate or severe comorbidity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
</tr>
<tr>
<td>0.020</td>
<td>0.020</td>
<td>0.020</td>
</tr>
<tr>
<td>0.029</td>
<td>0.029</td>
<td>0.029</td>
</tr>
</tbody>
</table>

*Adult comorbidity evaluation 27 (ACE-27)


10/12/2008
Cumulative Illness Rating Scale
Geriatric (CIRS–G)

<table>
<thead>
<tr>
<th>Rating strategy</th>
<th>0 = no problem</th>
<th>1 = current mild problem or past significant problem</th>
<th>2 = moderate disability or morbidity, requires first-line therapy</th>
<th>3 = severe/constant significant disability/uncontrollable chronic problems</th>
<th>4 = extremely severe/immediate treatment required/end organ failure/severe impairment in function</th>
</tr>
</thead>
</table>

Evaluation of dependence status in senior adults

**IADL**
- Get place at walking distance
- Use telephone
- Take medication
- Manage money

**ADL**
- Transfer
- Continence
- Going to toilet
- Bathing
- Dressing
- Feeding

One abnormality is significant

Chemotherapy in advanced prostate cancer

TAX 327: docetaxel shows a similar benefit in young and senior adults

And also…

- **Nutrition:**
  - Weight loss and body mass index
  - Serum albumin level
- **Cognition:**
  - Screening for memory impairment
- **Depression**
- **Polypharmacy**
- **Risk of falling**
  - Monopodal stay position
- **Caregiver**
175 senior adults (aged 75 to 90 years) treated with first line docetaxel-based therapy for metastatic HRPC:
- 95 patients (54%) had "standard" docetaxel regimen (70-75 mg/m² d1, q3w)
- 80 patients (46%) had "adapted" docetaxel regimen (30-35 mg/m² weekly)

<table>
<thead>
<tr>
<th></th>
<th>Adapted regimen (n=80)</th>
<th>Standard regimen (n=95)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA response*</td>
<td>68%</td>
<td>71%</td>
<td>0.79</td>
</tr>
<tr>
<td>Recist response</td>
<td>43%</td>
<td>40%</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*PSA decrease of 50% or more from baseline under treatment
- Median progression-free survival: 7.4 months
  (25.5% at 1 year, 5.1% at 2 years)
- Median overall survival: 15 months
  (59.3% at 1 year, 28.7% at 2 years)
- No significant trend between standard and adapted regimen

Grade 3-4 adverse events

Specific guidelines for management of senior adults with prostate cancer now ready for publication
- Systematic literature search
- Specific aspects pertaining to geriatrics
- The bibliographic material was reviewed and discussed by a scientific panel

- J.P. Droz (oncologist, France)
- L. Baldacci (oncologist, USA)
- M. Bolla (radiation oncologist, France)
- M. Emberton (urologist, UK)
- John Fitzpatrick (urologist, Ireland)
- S. Joniau & H. van Poppel (urologists, Belgium)
- S. Monfardini (oncologist, Italy)
- J. Moul (urologist, US)
- A. Naeim (oncologist, US)
- F. Saad (urologist, Canada)
- Cora Sternberg (oncologist, Italy)

Available at www.ejucancer.com

Journal homepage: www.eurourol.com

International Society of Geriatric Oncology (SIGO)
Proposals in Senior Adult Men


International Society of Geriatric Oncology (SIGO)
Proposal of guidelines for advanced prostate cancer in senior adults


Eau 2008
SIOG proposed recommendations

- The urological approach in senior adults with prostate cancer should be the same as in younger patients
- Internationally accepted guidelines (EAU, NCCN, AUA, etc.) are valid, as well as scientifically established national guidelines

Localized prostate cancer
Special considerations for senior adults

| D’AMICO risk classification | 10-year mortality in men 70+
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (PSA ≤ 10ng/ml and Gleason score ≤ 6 and T1c or T2a)</td>
<td>Overall: ~ 20% Due to prostate cancer: ~ 0%</td>
</tr>
<tr>
<td>Medium risk (PSA 10-20 mg/ml or Gleason 7 or T2b)</td>
<td>Overall: ~ 40% Due to prostate cancer: ~ 10%</td>
</tr>
<tr>
<td>High risk (PSA &gt;20ng/ml or Gleason score ≥7 or T2c)</td>
<td>Overall: ~ 60% Due to prostate cancer: ~ 30%</td>
</tr>
</tbody>
</table>

Only men within the high risk group have a significant 10-year mortality due to prostate cancer and are likely to receive curative treatment

Guideline: Localized prostate cancer

- Life expectancy evaluation
- Group 1 (Healthy)
  - Competence (CIS-R-G): grade 0 or 1
  - No malnutrition
  - Standard treatment as for younger patients

- Group 2 (Vulnerable, i.e. reversible problem)
  - Competence (CIS-R-G): at least one grade 2
  - No malnutrition
  - Standard treatment as for younger patients except prostatectomy

- Group 3 (Frail, i.e. non-reversible problem)
  - Competence (CIS-R-G): at least one grade 4
  - Terminal frailty: at least 1 ADL impaired
  - Symptom management including specific treatments (hormones, RTUP, etc.)

- Group 4 (Terminal illness)
  - Terminal frailty: Major comorbidities
  - Cognition impairment
  - Dehydration
  - Only palliative treatment

Guideline: Advanced prostate cancer

- Life expectancy evaluation
- Group 1 (Healthy)
  - Competence (CIS-R-G): grade 0 or 1
  - No malnutrition
  - Hormonal treatment (first and second lines, anti-androgen withdrawal, biphosphonates)

- Group 2 (Vulnerable, i.e. reversible problem)
  - Competence (CIS-R-G): at least one grade 2
  - No malnutrition
  - Standard chemotherapy

- Group 3 (Frail, i.e. non-reversible problem)
  - Competence (CIS-R-G): at least one grade 4
  - Terminal frailty: at least 1 ADL impaired
  - Cognition impairment
  - Adapted (weekly?) chemotherapy

- Group 4 (Terminal illness)
  - Terminal frailty: Major comorbidities
  - Cognition impairment
  - Symptomatic treatment

Advanced prostate cancer
Special considerations for senior adults

- Hormone-sensitive prostate cancer:
  - Androgen deprivation is the standard but induces bone loss
  - Baseline evaluation: bone mineral density + dosage Ca & Vitamin D3
  - Supplementation with calcium & vitamin D
  - Previous osteoporosis: biphosphonates

- Hormone-resistant prostate cancer:
  - Chemotherapy with docetaxel (75 mg/m² q3w) is the standard and shows the same efficacy in healthy senior adults as in younger patients.
  - The tolerability of weekly docetaxel has not been specifically studied in vulnerable and frail senior adults. (The place of weekly docetaxel in this setting should be further evaluated)
  - Palliative treatments as palliative surgery, radiopharmaceutics, radiotherapy, medical treatments for pain and symptoms

Work still in progress ...

- A set of references has been selected
- A first draft has been written and has circulated in the writing committee
- Guideline proposals have been presented in various meetings to obtain feedback opinion
- Extensive manuscript (a review) will be submitted this month to Critical Review in Hemato-Oncology on behalf of the SIOG Prostate Cancer Guidelines Task Force
- Abridged version will be submitted to BJU Int. this month
- Recommendations will be discussed in the setting of the different societies (ASCO, AUA, EAU, ASTRO, ESMO, ESTRO...). Production of consensus guidelines will be attempted. Validation to be proposed to the different national societies