International Society of Geriatric Oncology
Prostate Cancer Guidelines Proposals
in Senior Adult men.

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The SIOG task force on prostate cancer guidelines in senior adults

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BACKGROUND

- The incidence of prostate cancer increases with age, with a median age at diagnosis of 68 years\textsuperscript{1}.
- Due to the increased life expectancy in developed countries, prostate cancer represents a major public health problem.
- Management of prostate cancer in senior adult men (\textgreater{} 70 years) is an important challenge for the future. No specific guidelines have been published at yet for this population.
- The SIOG (International Society of Geriatric Oncology) has developed a proposal for recommendations in this setting.

MATERIAL & METHODS

- A systematic literature search focused on screening, diagnosis procedures, and treatment options for localized, locally advanced and metastatic prostate cancer in senior adults was done.
- Specific aspects pertaining to a geriatric population were emphasized and included: evaluation of health status (nutritional, cognitive, thymic, physical and psycho-social evaluations) and screening for vulnerability and frailty.
- Particular attention was given to the consequences of androgen deprivation and complications of local treatment (i.e. incontinence).
- The bibliographic material was reviewed and discussed by a scientific panel which included urologists, radiation oncologists, medical oncologists and geriatricians from both Europe and North America.
Special considerations for health status evaluation
Life expectancy in senior adults: a large variability reflecting health status variability

Practical Geriatric Assessment (1)

- Clinical examination
- Pharmaceutical assessment
- Comorbidities
- Specific questionnaire (including QoL)
- Biological screening:
  - Hemogram, liver tests, creatinine clearance, Ca & Ph
  - TSH & LT4, vitamine B 12, folic acid, vitamin D3
  - Albumin & pre-albumin.
Comorbidity evaluation: the choice of CISR-G

**Charlson comorbidity index**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Present</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarct</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td>1</td>
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<tr>
<td>Peripheral vascular disease</td>
<td></td>
<td>1</td>
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<tr>
<td>Cerebrovascular disease (except hemiplegia)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td></td>
<td>1</td>
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<tr>
<td>Connective tissue disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diabetes (without complications)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diabetes with end organ damage</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
<td></td>
<td>2</td>
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<tr>
<td>2nd solid tumor (non metastatic)</td>
<td></td>
<td>2</td>
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<tr>
<td>Leukemia</td>
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<td>2</td>
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<tr>
<td>Lymphoma, multiple myeloma...</td>
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<tr>
<td>Moderate or severe liver disease</td>
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<td>3</td>
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<tr>
<td>2nd metastatic solid tumor</td>
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<td>6</td>
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<tr>
<td>AIDS</td>
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</table>

**TOTAL POINTS**

**CISR-G**

<table>
<thead>
<tr>
<th>Score</th>
<th>Heart</th>
<th>Vascular</th>
<th>Haematopoietic</th>
<th>Respiratory</th>
<th>Eyes, Ears, Nose, Throat &amp; Larynx</th>
<th>Upper GI</th>
<th>Lower GI</th>
<th>Liver</th>
<th>Renal</th>
<th>Genitourinary</th>
<th>Musculoskeletal/Integument</th>
<th>Neurological</th>
<th>Endocrine/Metabolic &amp; Breast</th>
<th>Psychiatric Illness</th>
<th>Total Number of Categories Endorsed</th>
<th>Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HEART</td>
<td>VASCULAR</td>
<td>HAEMATOPOIETIC</td>
<td>RESPIRATORY</td>
<td>EYES, EARS, NOSE, THROAT &amp; LARYNX</td>
<td>UPPER GI</td>
<td>LOWER GI</td>
<td>LIVER</td>
<td>RENAL</td>
<td>GENITOURINARY</td>
<td>MUSCULOSKELETAL/INTEGUMENT</td>
<td>NEUROLOGICAL</td>
<td>ENDOCRINE/METABOLIC &amp; BREAST</td>
<td>PSYCHIATRIC ILLNESS</td>
<td>TOTAL NUMBER OF CATEGORIES ENDORSED</td>
<td>TOTAL SCORE</td>
</tr>
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<td></td>
<td></td>
<td>0 - no problem; 1 - Current mild problem or past significant problem; 2 - Moderate disability or morbidity/ requires &quot;first line&quot; therapy; 3 - Severe/constant significant disability/ uncontrollable chronic problems; 4 - Extremely severe/immediate treatment required/end organ failure/severe impairment in function</td>
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Practical Geriatric Assessment (2)

• Measure of geriatric scales:
  – Dependancy: ADL & IADL,
  – Nutrition: MNA, weight loss > 5%
  – Depression: GDS
  – Cognition: MMS, repeated delirium, dementia
  – Risk of fall: Tinetti test

• Geriatric syndromes include: dementia, delirium, depression, falls, neglect and abuse, spontaneous bone fractures

• Metabolis syndrom (diabetes type II+++)}
Special considerations for prostate cancer
Localized prostate cancer

Radical prostatectomy
Radiation therapy

Only patients with high-risk disease are likely to receive curative treatment

<table>
<thead>
<tr>
<th>D’AMICO RISK CLASSIFICATION(^\text{12})</th>
<th>10-YEAR MORTALITY IN MEN 70+</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 ng/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 &gt;7 or T2c)</td>
<td>Overall: ≈ 60% Due to prostate cancer: ≈ 30%</td>
</tr>
</tbody>
</table>

- Death of other causes
- Death of prostate cancer

D’Amico A et al. JCO 2003, 21: 2163-2172
It included 8275 patients from 27 randomized trials, 88% of patients had metastatic and 12% locally advanced disease; the median age was 70 years and the median follow-up was 5 years. A 1.8% 5-year survival gain was observed with CAB but failed to reach statistical significance.

Androgen suppression increases the risk of fracture

Randomized Controlled Trial of Annual Zoledronic Acid to Prevent Gonadotropin-Releasing Hormone Agonist–Induced Bone Loss in Men With Prostate Cancer

M. Dror Michaelson, Donald S. Kaufman, Hang Lee, Francis J. McGovern, Philip W. Kantoff, Mary Anne Fallon, Joel S. Finkelstein, and Matthew R. Smith

Fig 1. Mean ± SE changes from baseline for (A) serum N-telopeptide and (B) serum bone alkaline phosphatase. P values are for between-group comparisons of the percent change from baseline to month 12.

**Mean change in serum N-telopeptide**

**Mean change in serum bone alkaline phosphatase**

**Conclusion**

In men receiving a GnRH agonist, a single treatment with zoledronic acid significantly increased BMD and durably suppressed serum N-telopeptide levels for 12 months. Annual zoledronic acid may be a convenient and effective strategy to prevent bone loss in hypogonadal men.
NCCN Recommendations

Monitor/Surveillance
- Patients being treated with either medical or surgical castration are at risk for having or developing osteoporosis. A baseline bone mineral density study should be considered in this group of patients, especially if long-term ADT is planned.
- Supplementation with calcium (500mg daily) and vitamin D (400 IU) is recommended for all men on long-term ADT.
- Men who are osteopenic/osteoporotic should be strongly considered for bisphosphonate therapy with zoledronic acid, pamidronate, alendronate, raloxifene or toremifene.

• Basic BMD. + dosage Ca & Vitamine D3
• Supplémentation with calcium & vitamine D:
  – Cholécalciférol (vit D3) 100,000 U/ 1 à 3 months.
  – Calcium : 500 mg à 1g / d. (serum Ca control).
• Previous ostéoporosis : biphosphonates
  Dose is debatable.
  Take care of toxicity (maxillary necrosis).
Stratification:

**Pain score**
- PSc ≥ 2 ou AS ≥ 10 versus PSc < 2 ou AS < 10
- KI ≤ 70 versus ≥ 80

**Randomization**

- **Docetaxel 75 mg/m² Q3 weeks** + prednisone 5 mg x 2/d
- **Docetaxel 30 mg/m² weekly 5/6 weeks.** + prednisone 5 mg x 2/d
- **Mitoxantrone 12 mg/m² Q3 weeks** + prednisone 5 mg x 2/d

**Treatment Duration:** 30 weeks

**TAX 327: Docetaxel in metastatic HRPC**

Results in the general case: TAX 327

1- Mitoxantrone plus prednisone was standard CT in HRPC.

2- Docetaxel has demonstrated a significant survival benefit.

3- Docetaxel is now accepted as the standard chemotherapy in HRPC.

The case of senior adults: TAX 327
Survival benefit for all age subgroups

But trial population is not representative of a senior adult population.

Hazard ratio in favour of Docetaxel Mitoxantrone

<table>
<thead>
<tr>
<th>ITT</th>
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<tbody>
<tr>
<td>Age &lt;65 years</td>
</tr>
<tr>
<td>Age ≥65 years</td>
</tr>
<tr>
<td>Age ≥75 years</td>
</tr>
<tr>
<td>Pain: no</td>
</tr>
<tr>
<td>Pain: yes</td>
</tr>
<tr>
<td>KPS ≥80</td>
</tr>
<tr>
<td>KPS ≤70</td>
</tr>
</tbody>
</table>

Weekly Docetaxel in Elderly Patients with Prostate Cancer: Efficacy and Toxicity in Patients at Least 70 Years of Age Compared with Patients Younger than 70 Years

Tomasz M. Beer¹
William Berry²
Emily M. Wersinger¹
Lisa B. Bland¹

Abstract
We sought to determine whether age was significantly associated with efficacy and toxicity of weekly docetaxel in patients with metastatic androgen-independent prostate cancer (AIPC). Individual patient data were pooled from 2 phase II clinical trials of weekly docetaxel 36 mg/m² for 6 of every 8 weeks in men with metastatic AIPC. Baseline chara-

Pooled analysis of 2 phase II clinical studies of weekly Taxotere (36mg/m² for 6/8 weeks) in men with metastatic androgen-independant prostate cancer

**Weekly docetaxel (Beer et al.) efficacy results: same activity**

<table>
<thead>
<tr>
<th></th>
<th>&lt; 70 years (n=34)</th>
<th>≥ 70 years (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECOG performance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17.6%</td>
<td>23.1%</td>
</tr>
<tr>
<td>1</td>
<td>55.9%</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>23.5%</td>
<td>26.9%</td>
</tr>
<tr>
<td>3</td>
<td>2.9%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median [95% CI]</td>
<td>45 weeks [36-54]</td>
<td>33 weeks [13-54]</td>
</tr>
<tr>
<td><strong>PSA response rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[95% CI]</td>
<td>40% 23%-57%</td>
<td>47% 33%-61%</td>
</tr>
<tr>
<td><strong>Measurable disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>progression rate [95% CI]</td>
<td>33% [0-66%]</td>
<td>29% [0-65%]</td>
</tr>
</tbody>
</table>

No significant differences for all parameters
Weekly docetaxel (Beer et al.) hematologic toxicity: few differences

<table>
<thead>
<tr>
<th></th>
<th>&lt; 70 years (n=34)</th>
<th>≥ 70 years (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>5.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>2.9%</td>
</tr>
<tr>
<td>Infection</td>
<td>5.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>14.7%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.9%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

No significant differences for all parameters
Decision trees

Internationally accepted guidelines (EAU, NCCN…) are valid as well as scientifically established national guidelines
### EAU guidelines for the management of localized prostate cancer

#### Stage T1a
- **Treatment**: Watchful waiting
- **Comment**: Standard treatment for well- and moderately differentiated tumors and < 10-year life expectancy. In patients with >10-year life expectancy, re-staging with TRUS and biopsy is advised (grade B recommendation)
- **Radical prostatectomy**: Optional in young patients with a long life expectancy, especially for poorly differentiated tumors (grade B recommendation)
- **Radiotherapy**: Optional in younger patients with a long life expectancy, especially for poorly differentiated tumors. Higher complication risks after TURP, especially with interstitial radiation (grade B recommendation)
- **Hormonal**: Not an option (grade A recommendation)
- **Combination**: Not an option (grade C recommendation)

#### Stage T1b-T2a
- **Watchful waiting**: Asymptomatic patients with well- and moderately differentiated tumors and a life expectancy < 10 years. Patients who do not accept treatment-related complications (grade B recommendation)
- **Radical prostatectomy**: Standard treatment for patients with life expectancy > 10 years who accept treatment-related complications (grade A recommendation)
- **Radiotherapy**: Patients with a life expectancy > 10 years who accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with 5-10 years of life expectancy and poorly differentiated tumors (combination therapy is recommended; see below) (grade B recommendation)
- **Hormonal**: Symptomatic patients who need palliation of symptoms unfit for curative treatment (grade C recommendation). Antiandrogens are associated with poorer outcome in comparison with watchful waiting are not recommended (grade A recommendation)
- **Combination**: Neoadjuvant hormonal therapy (NHT) + radical prostatectomy: no proven benefit (grade A recommendation). NHT + radiotherapy: better local control. No proven survival benefit (grade B recommendation). Hormonal (3 years) + radiotherapy: better than radiotherapy in poorly differentiated tumors (grade A recommendation).

#### Stage T3-T4
- **Watchful waiting**: Option in asymptomatic patients with T3, well-differentiated and moderately differentiated tumors, and a life expectancy < 10 years (grade C recommendation)
- **Radical prostatectomy**: Optional for selected patients with T3a and a life expectancy > 10 years (grade C recommendation)
- **Radiotherapy**: T3 with > 5 10 years of life expectancy. Dose escalation > 70 Gy seems to be of benefit. If this is not available, a combination with hormonal therapy could be recommended (see below) (grade A recommendation)
- **Hormonal**: Symptomatic patients, extensive T3-T4, high PSA level (>25 ng/mL), unfit patients. Better than watchful waiting (grade A recommendation)
- **Combination**: Radiotherapy + hormonal seems better than radiotherapy alone (grade A recommendation). NHT + radical prostatectomy: no proven benefit (grade B recommendation)

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EAU guidelines on prostate cancer, 2007 update (EAU website);
### EAU guidelines for the management of advanced prostate cancer

#### Summary of hormonal therapy (ADT):

1. In advanced prostate cancer, ADT delays progression, prevents potentially catastrophic complications and effectively palliates symptoms, but does not prolong survival (level of evidence: 1b)

2. In advanced prostate cancer, all forms of castration as monotherapy (orchiectomy, LHRH and DES) have equivalent therapeutic efficacy (level of evidence: 1b)

3. Non-steroidal antiandrogen monotherapy (e.g. bicalutamide) is an effective alternative to castration in patients with locally advanced disease (level of evidence: 1b)

4. In advanced prostate cancer, the addition of a non-steroidal antiandrogen to castration (CAB) results in a small advantage in overall survival over castration alone but is associated with increased adverse events, reduced quality of life and high costs (level of evidence: 1a)

5. Intermittent and "minimal" ADT should still be regarded as experimental therapies (level of evidence: 3)

6. In advanced prostate cancer, immediate (given at diagnosis) androgen suppression significantly reduces disease progression and complication rate due to progression itself compared to deferred (delivered at symptomatic progression) androgen deprivation (level of evidence: 1b)

7. Bilateral orchiectomy may be the most cost-effective form of ADT, especially if initiated after occurrence of symptoms from metastatic disease (level of evidence: 3)

#### Guidelines & recommendations for cytotoxic therapy in hormono-refractory prostate cancer (HRPC):

1. In patients with a PSA rise only, 2 consecutive increases of PSA serum levels above a previous reference level should be documented (grade B recommendation)

2. Prior to treatment, PSA serum levels should be >5ng/mL to assure correct interpretation of therapeutic efficacy (grade B recommendation)

3. Potential benefits of cytotoxic therapy and expected side effects should be discussed with each individual patient (grade C recommendation)

4. In patients with metastatic HRPC, and who are candidates for cytotoxic therapy, docetaxel at 75 mg/m² every 3 weeks has shown a significant survival benefit (grade A recommendation)

5. In patients with symptomatic osseous metastases due to HRPC, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options (grade A recommendation)
Senior adults with localized prostate cancer

Life Expectancy Evaluation

**Group 1** (Healthy)
- Comorbidity (CISR-G): grade 0 or 1 or 2
- Independent in IADL
- No denutrition

**Group 2** (Vulnerable, i.e. reversible problem)
- Comorbidity (CISR-G): at least one grade 3
- Dependent in ≥ 1 IADL
- Denutrition

**Group 3** (Frail, i.e. non reversible problem)
- Comorbidity (CISR-G): several grade 3 or at least one grade 4
- Dependency: Impairment of at least one ADL
- Cognitive impairment
- Repeated delirium
- Severe denutrition

**Group 4** (Terminal illness)
- Terminal
- Bedridden
- Major comorbidities
- Cognitive impairment

Standard treatment as for younger patients

Standard treatment as for younger patients except prostatectomy

Symptomatic management including specific treatments (hormones, RTUP...)

Only palliative treatment

Readaptation
Senior adults with advanced prostate cancer

**Life Expectancy Evaluation**

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- Cognitive impairment
- Repeated delirium
- Severe denutrition

**Group 4** (Terminal illness)
- Terminal
- Bedridden
- Major comorbidities
- Cognitive impairment

**Hormonal treatment** (first & second lines, anti-androgen withdrawal, biphosphonates.)

- Standard chemotherapy
- Standard chemotherapy
- Adapted (weekly?) chemotherapy
- Symptomatic treatment

**Readaptation**
Guidelines

- The **urological approach** in senior adults with prostate cancer is **the same as in younger patients**.
- Internationally accepted guidelines are used.
- Stratification of patients with localized disease use the **D’Amico classification**. Only **high-risk** patients are likely to benefit from curative therapy.
- Treatment decisions should be based on **evaluation of patient “health status”**:
  - “**Fit**” or healthy senior adults should receive the same treatment as **younger patients**.
  - “**Vulnerable**” patients (who have reversible impairment) should receive standard treatment after readaptation.
  - “**Frail**” patients (who have non-reversible impairment) should receive adapted treatment.
  - “**Too sick**” patients are candidates for symptomatic treatments.
Communication strategy

• Congress presentations:
  – ECCO 14th meeting (Barcelona) in october 2007
  – SIOG (Madrid) in november 2007
  – Submitted to:
    • GU ASCO meeting, San Francisco (February 2008).
    • EAU meeting in Milan (march 2008).
    • Will be submitted to ASCO annual meeting, AUA and ASTRO

• Publications: CROH (review of the material), BJU Int. after external review.