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

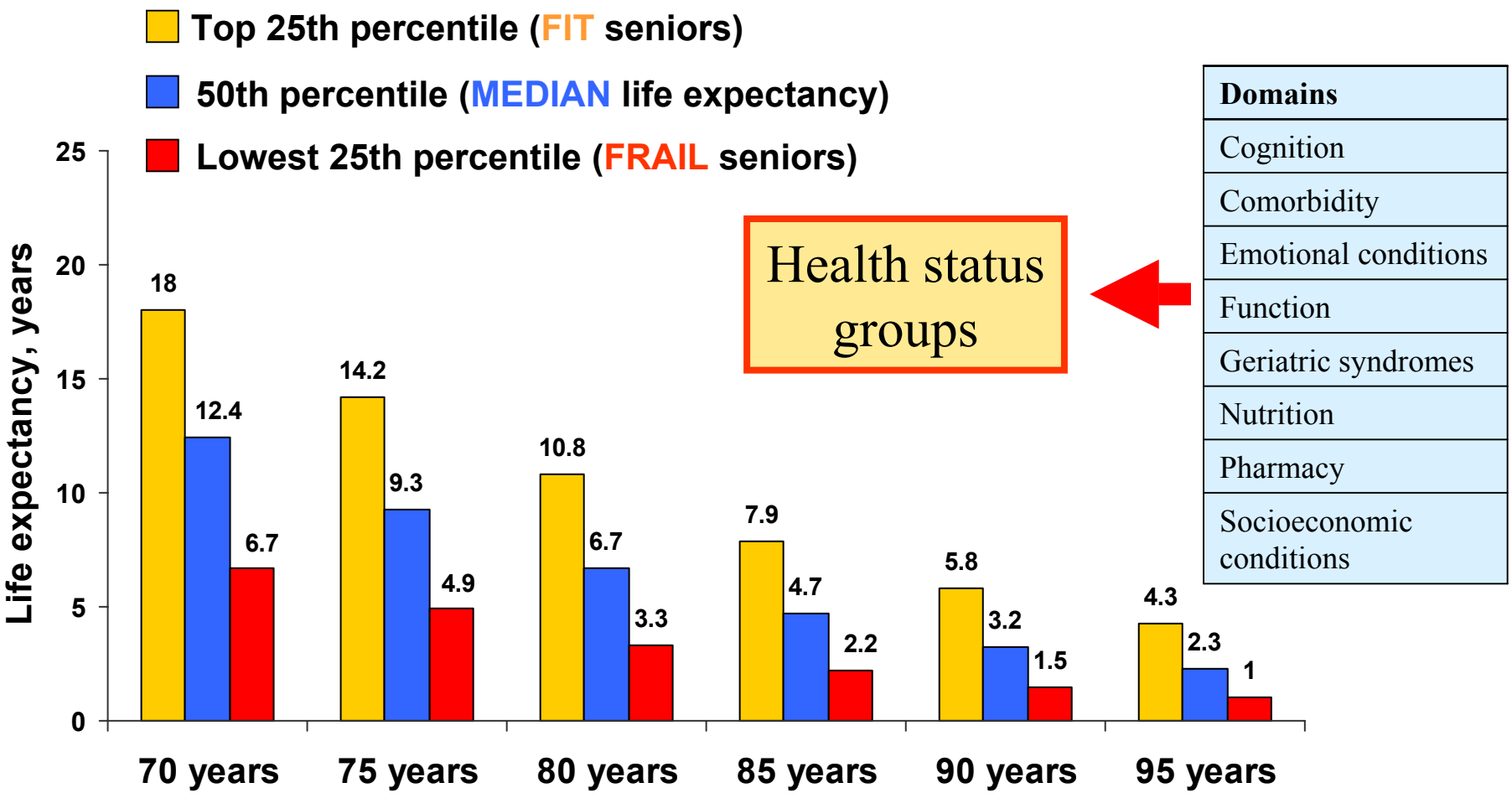
- The incidence of prostate cancer increases with age, with a median age at diagnosis of 68 years[1].
- Due to the increased life expectancy in developed countries, prostate cancer represents a major public health problem.
- Management of prostate cancer in senior adult men (> 70 years) is an important 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



Walter LC et al. *JAMA* 2001, 285, 2750-2756

Practical Geriatric Assessment (1)

- **Clinical examination**
- Pharmaceutical assessement
- **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[3]

COMORBIDITY	PRESENT	POINTS
Myocardial infarct		1
Congestive heart failure		1
Peripheral vascular disease		1
Cerebrovascular disease (except hemiplegia)		1
Dementia		1
Chronic pulmonary disease		1
Connective tissue disease		1
Ulcer disease		1
Mild liver disease		1
Diabetes (without complications)		1
Diabetes with end organ damage		2
Hemiplegia		2
Moderate or severe renal disease		2
2nd solid tumor (non metastatic)		2
Leukemia		2
Lymphoma, multiple myeloma…		2
Moderate or severe liver disease		3
2nd metastatic solid tumor		6
AIDS		6
TOTAL POINTS		

CISR-G[7]

	Score
HEART	
VASCULAR	
HAEMATOPOIETIC	
RESPIRATORY	
EYES, EARS, NOSE, THROAT & LARYNX	
UPPER GI	
LOWER GI	
LIVER	
RENAL	
GENITOURINARY	
MUSCULOSKELETAL/INTEGUMENT	
NEUROLOGICAL	
ENDOCRINE/METABOLIC & BREAST	
PSYCHIATRIC ILLNESS	
TOTAL NUMBER OF CATEGORIES ENDORSED	
TOTAL SCORE	
Severity index (total score/ total number of categories endorsed)	
Number of categories at level 3 severity	
Number of categories at level 4 severity	

RATING STRATEGY: 0= no problem; 1= Current mild problem or past significant problem; 2= Moderate disability or morbidity/ requires "first line" therapy; 3= Severe/constant significant disability/ uncontrollable chronic problems; 4= Extremely severe/immediate treatment required/end organ failure/severe impairment in function

(3) Charlson ME et al J. Chronic. Dis. 1987, 40: 373-83.

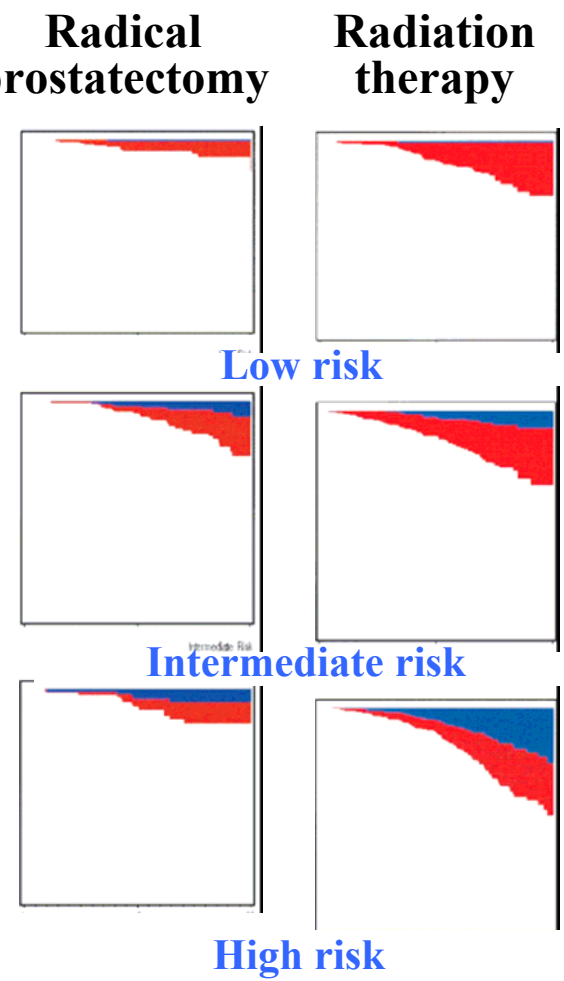
(7) Miller MD et al. Psychiatry Res, 1992; 41: 237-48.

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



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

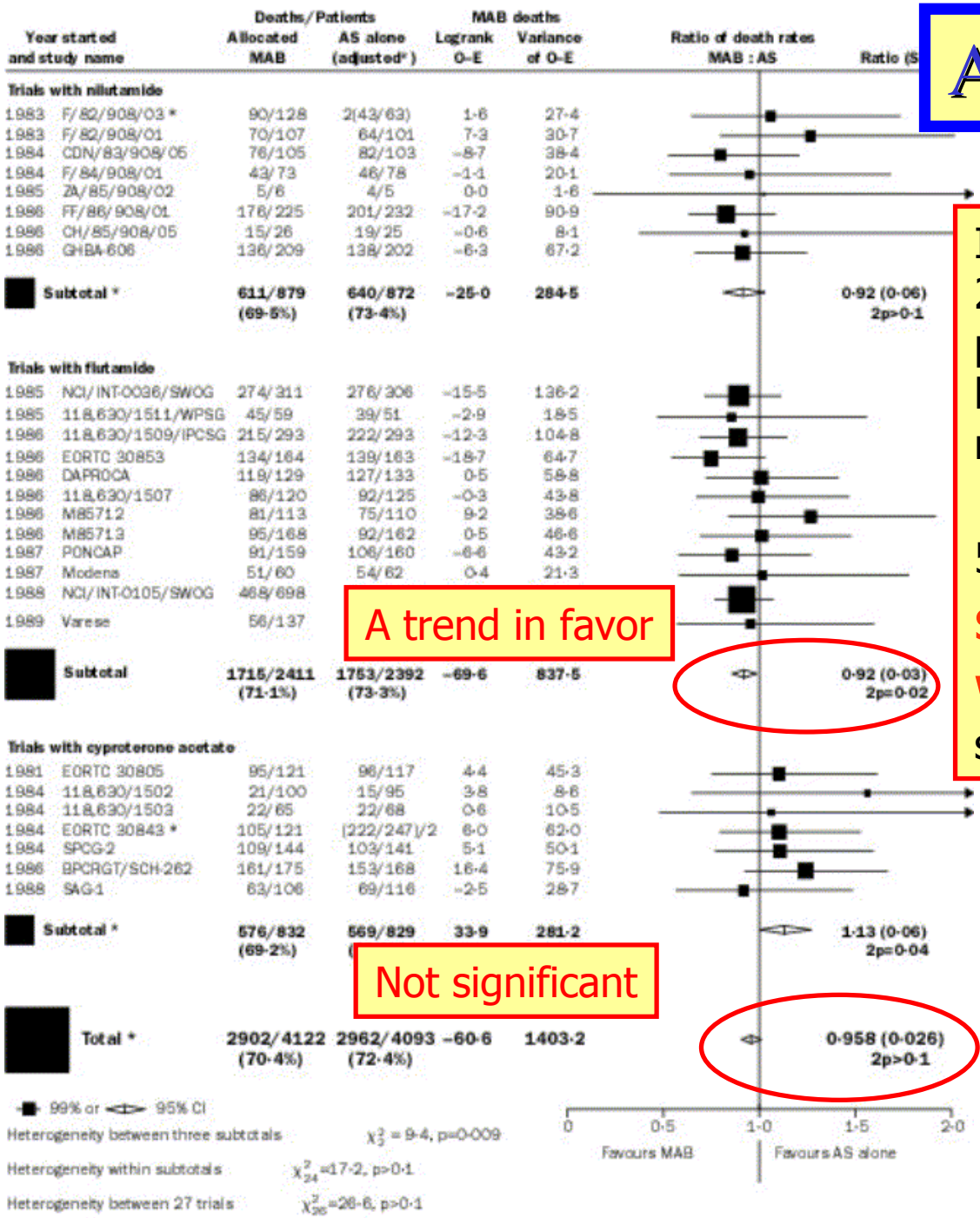
D'Amico risk classification[12]	10-year Mortality in men 70+
Low risk (PSA ≤ 10ng/ml and Gleason score ≤ 6 and T1c or T2a)	Overall: ≈ 20% Due to prostate cancer: ≈ 0%
Medium risk (PSA 10-20 ng/mL or Gleason = 7 or T2b)	Overall: ≈ 40% Due to prostate cancer: ≈ 10%
High risk (PSA >20ng/mL or Gleason score >7 or T2c)	Overall: ≈ 60% Due to prostate cancer: ≈ 30%

Death of other causes

Death of prostate cancer

D'Amico A et al. *JCO* 2003, 21: 2163-2172

Androgen deprivation.



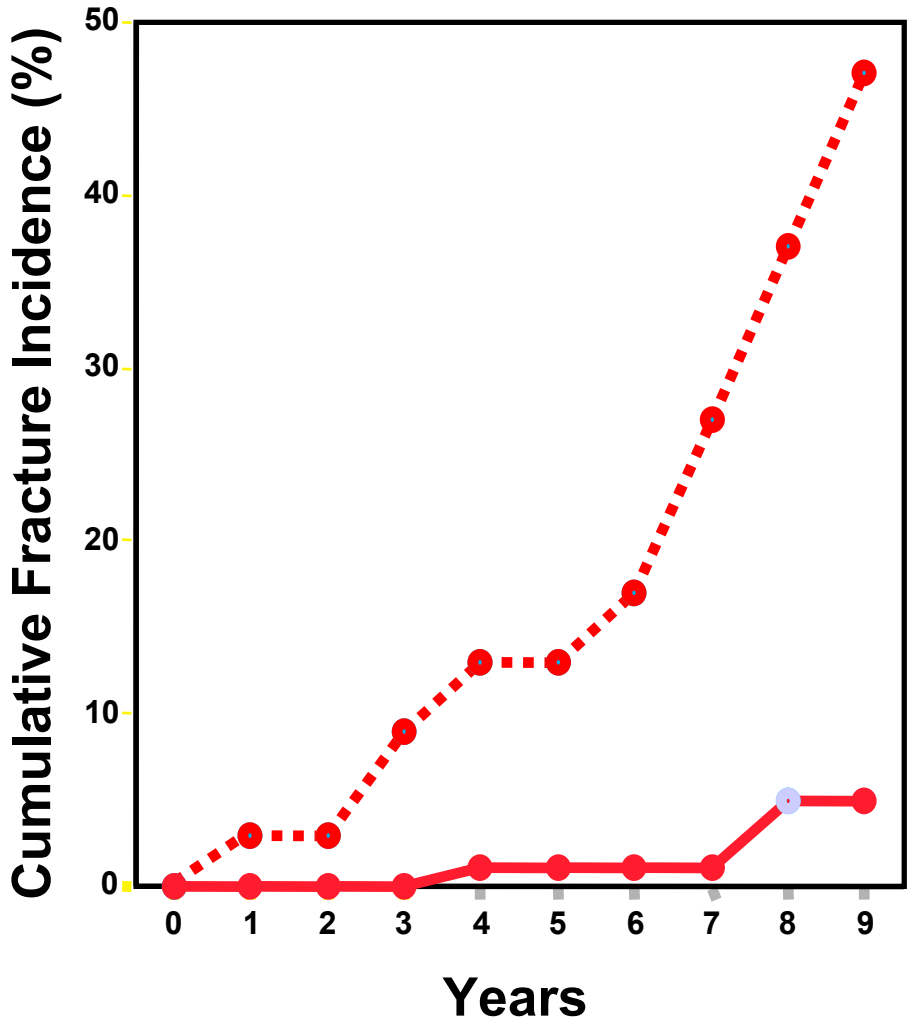
A trend in favor

Not significant

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.

Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet 2000, 355, 1491-1498.

Androgen suppression increases the risk of fracture



Daniell et al. *J Urol*. 1997;157:439-444.

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

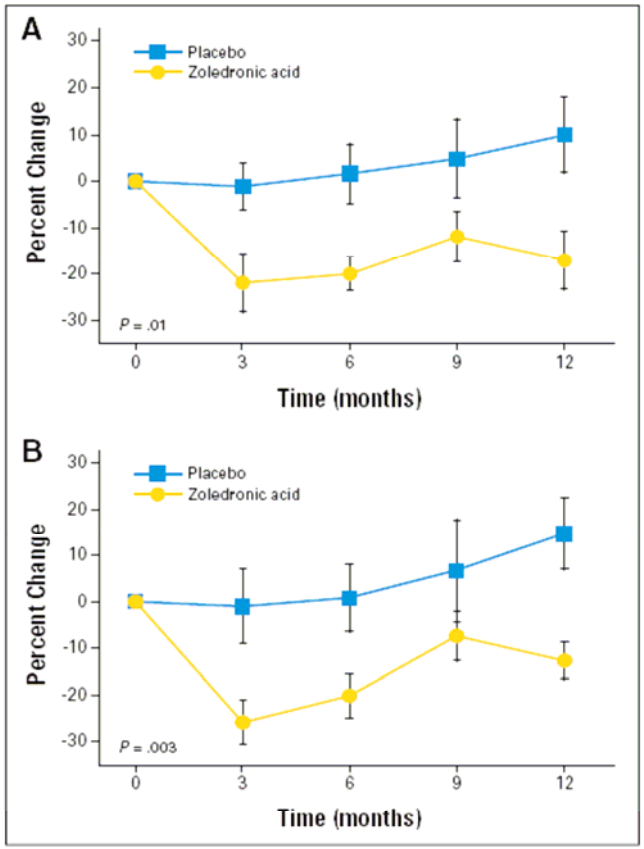


Fig 1. Mean (± SE) changes from baseline for (A) serum N-telopeptide and (B) serum bone alkaline phosphatase. *P* values are for between-group comparisons of the percent change from baseline to month 12.

Mean change in serum N-telopeptide

Mean change in serum bone alcaline 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.

J Clin Oncol 25:1038-1042. © 2007 by American Society of Clinical Oncology

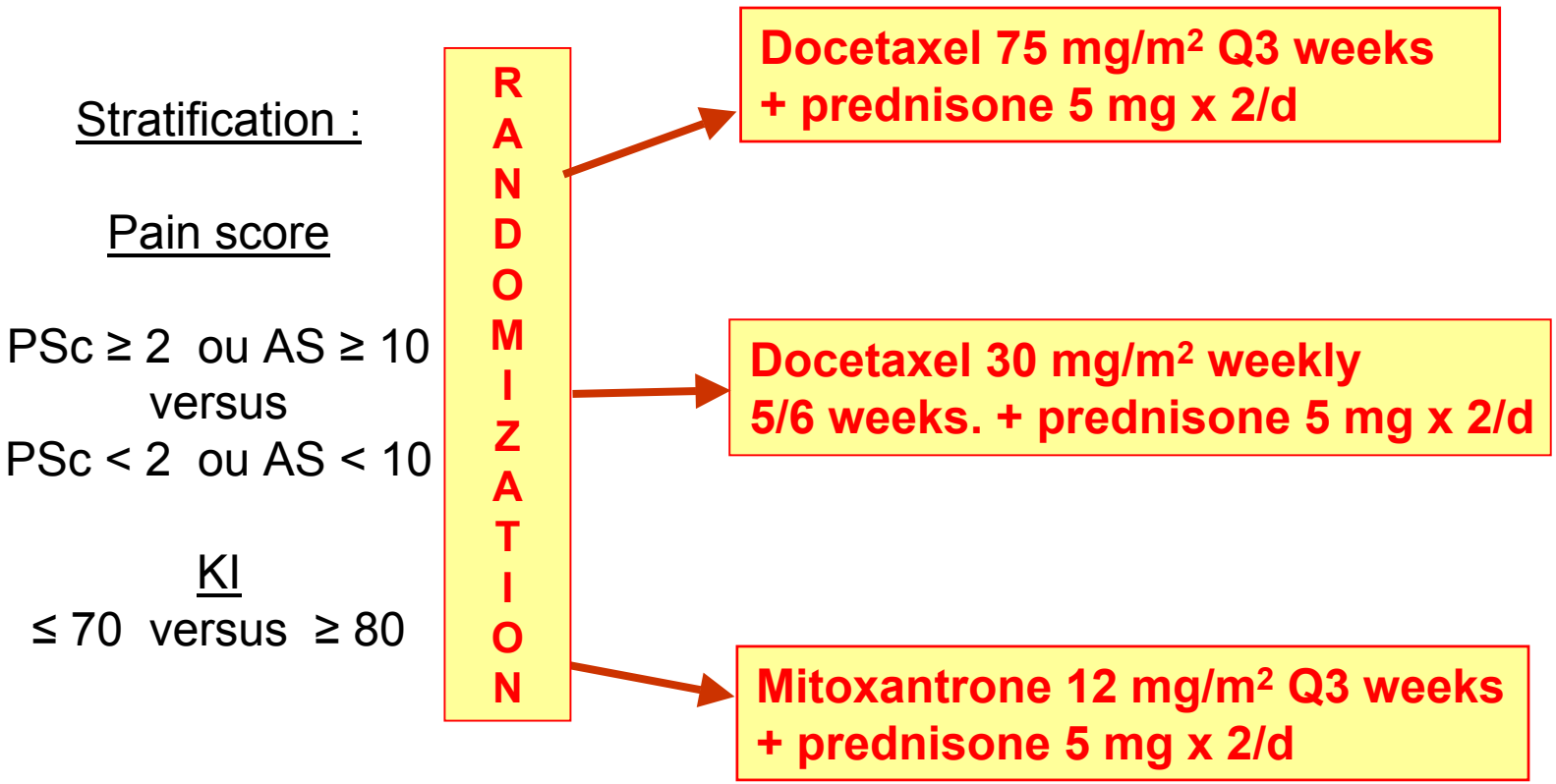
NCCN Recommendations

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 patient, especially if longterm 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).



Treatment Duration : 30 weeks

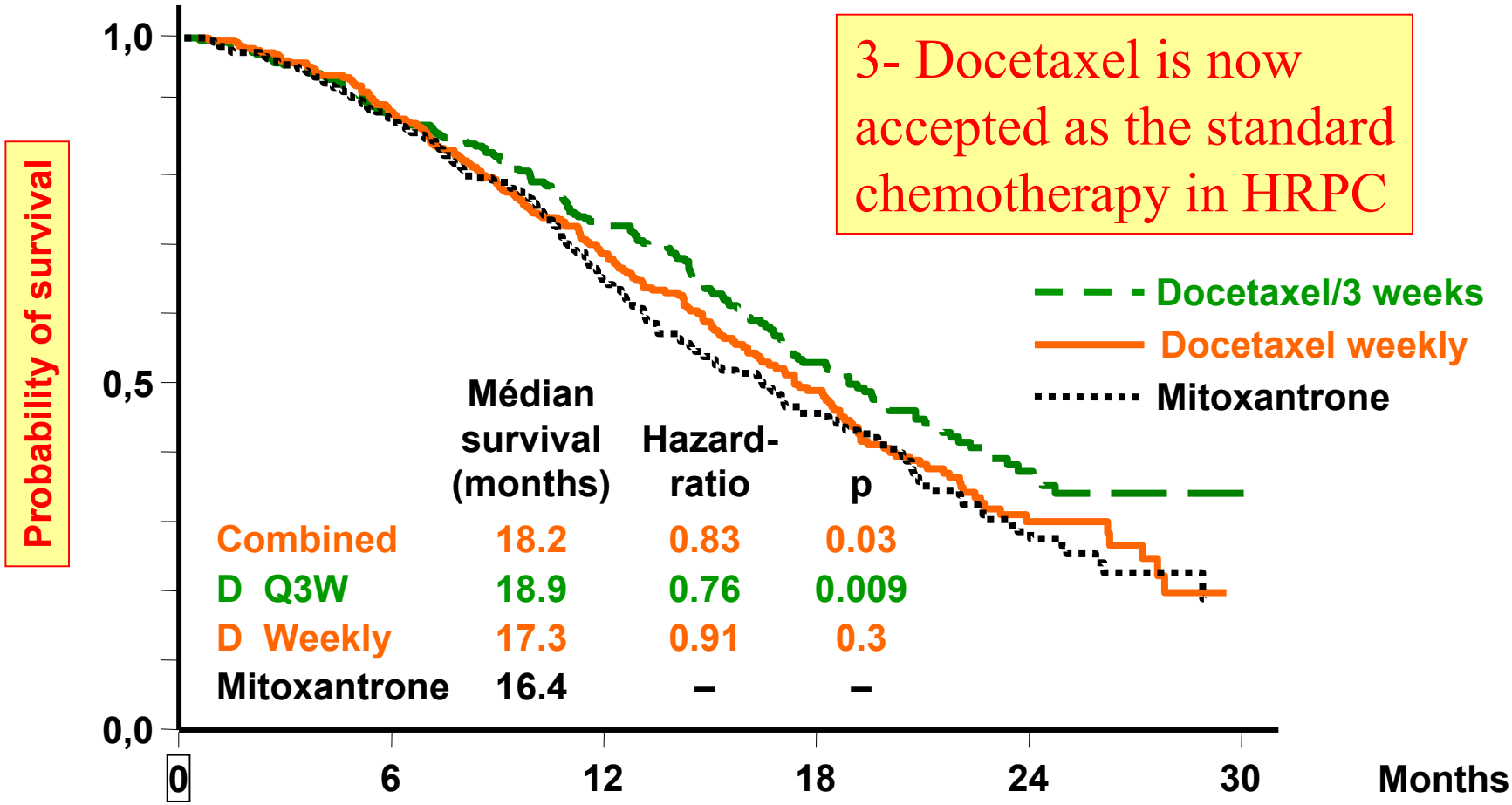
TAX 327: Docetaxel in metastatic HRPC

Tannock IA et al. *N Engl J Med* 2004, 351: 1502-1512

Results in the general case: TAX 327

1- Mitoxantrone plus prednisone was standard CT in HRPC.

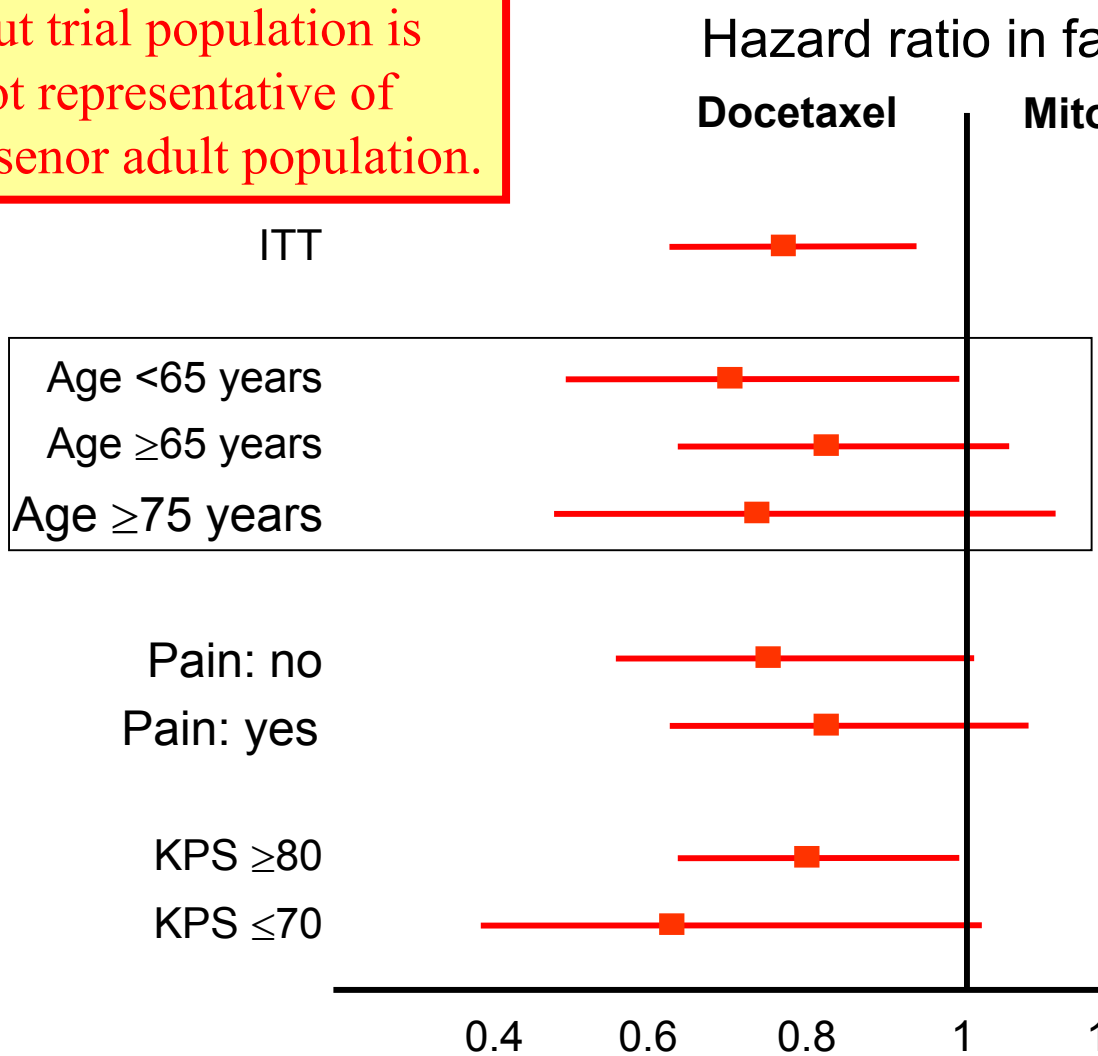
2- Docetaxel has demonstrated a significant survival benefit



Tannock IA et al. *N Engl J Med* 2004, 351: 1502-1512

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

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



Docetaxel trial	Elderly pts population
Normal cardiac function	Incidence severe CHF: 1.5%* Prevalence CHF: 13%
No serious medical condition	Median CIRS-G score: 12
Age > 75 years : # 20%	50 %
Karnofsky < 70 : # 10%	50 %
Creat < 1.5 x N	50 % with Creatinine Clearance < 50 ml/mn

Tannock IF, *et al. N Engl J Med* 2004; 351: 1502–1512.

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. Beer[1]
William Berry[2]
Emily M. Wersinger[1]
Lisa B. Bland[1]

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/m^2 for 6 of every 8 weeks in men with metastatic AIPC. Baseline charac-

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

Beer TM, Berry W et al. *Clinical prostate cancer* 2003, 2: 167-172

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

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

No significant differences for all parameters

Weekly docetaxel (Beer et al.) hematologic toxicity: few differences

	< 70 years (n=34)		≥ 70 years (n=52)	
	Grade 2	Grade ≥3	Grade 2	Grade ≥3
Leucopenia	5.9%	2.9%	1.9%	5.8%
Neutropenia	0	2.9%	0	3.8%
Infection	5.9%	0%	3.8%	11.5%
Anemia	14.7%	8.8%	5.8%	5.8%
Thrombocytopenia	2.9%	2.9%	3.8%	1.9%

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[11]

Stage	Treatment	Comment
T1a	Watchful waiting	Standard treatment for well-, and moderately diffentiated 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)
T1b-T2b	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 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).
T3-T4	Watchful waiting	Option in asymptomatic patients with T3, well-differentiated and moderately diffentiated 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)

EAU guidelines on prostate cancer, 2007 update (EAU website);

EAU guidelines for the management of advanced prostate cancer[11]

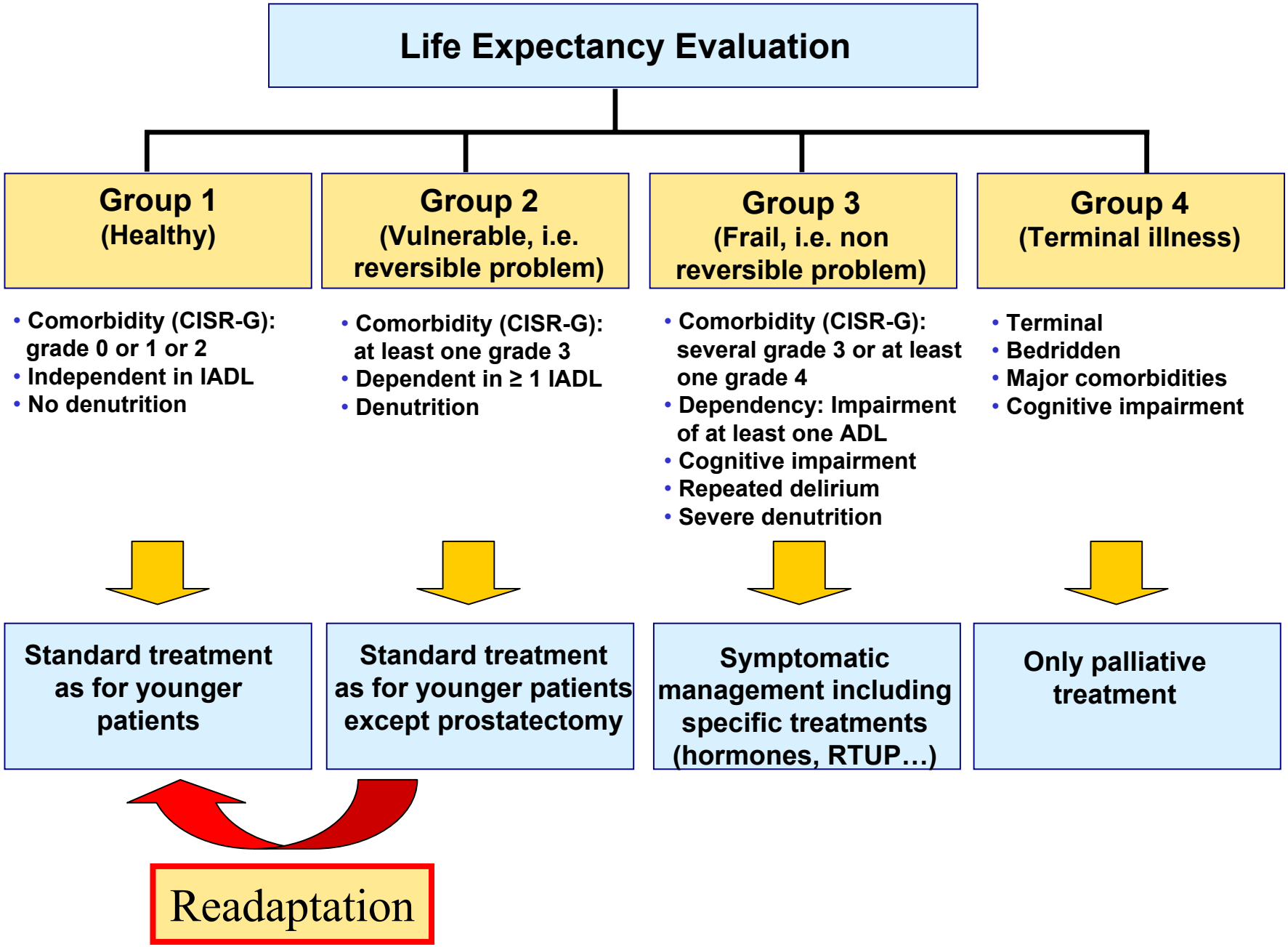
Summary of hormonal therapy (ADT):

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)

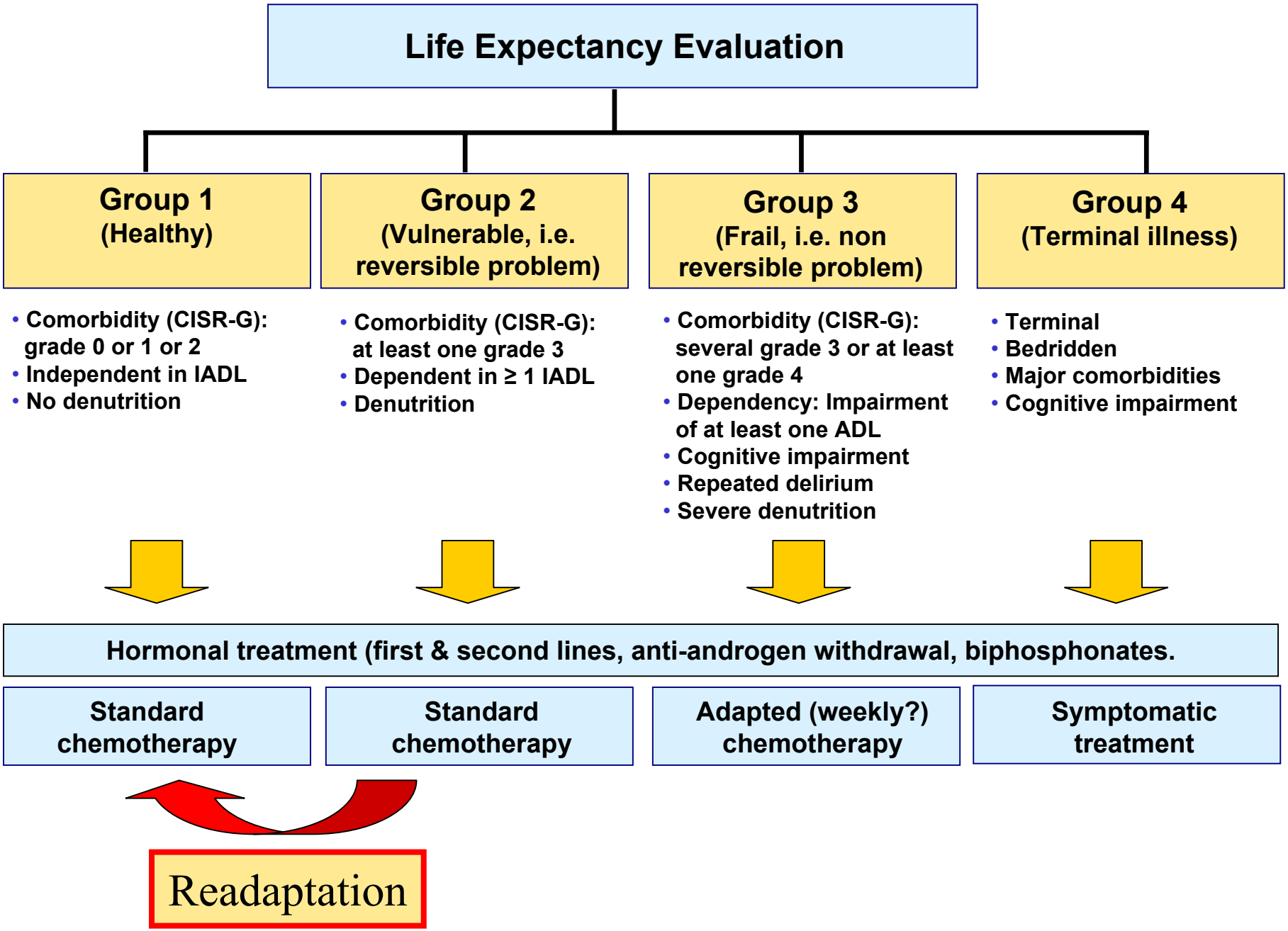
Guidelines & recommendations for cytotoxic therapy in hormono-refractory prostate cancer (HRPC):

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/m^2 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



Senior adults with advanced prostate cancer



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 :
  - SIU (Paris) in september 2007.
  - EPOG (French Society OncoGeriatrics, Bordeaux) in september 2007.
  - 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 sumitted to ASCO annual meeting, AUA and ASTRO
- Publications : CROH (review of the material), BJU Int. after external review.