Clinically Insignificant Prostate Cancers:
"*Are they really insignificant?*"

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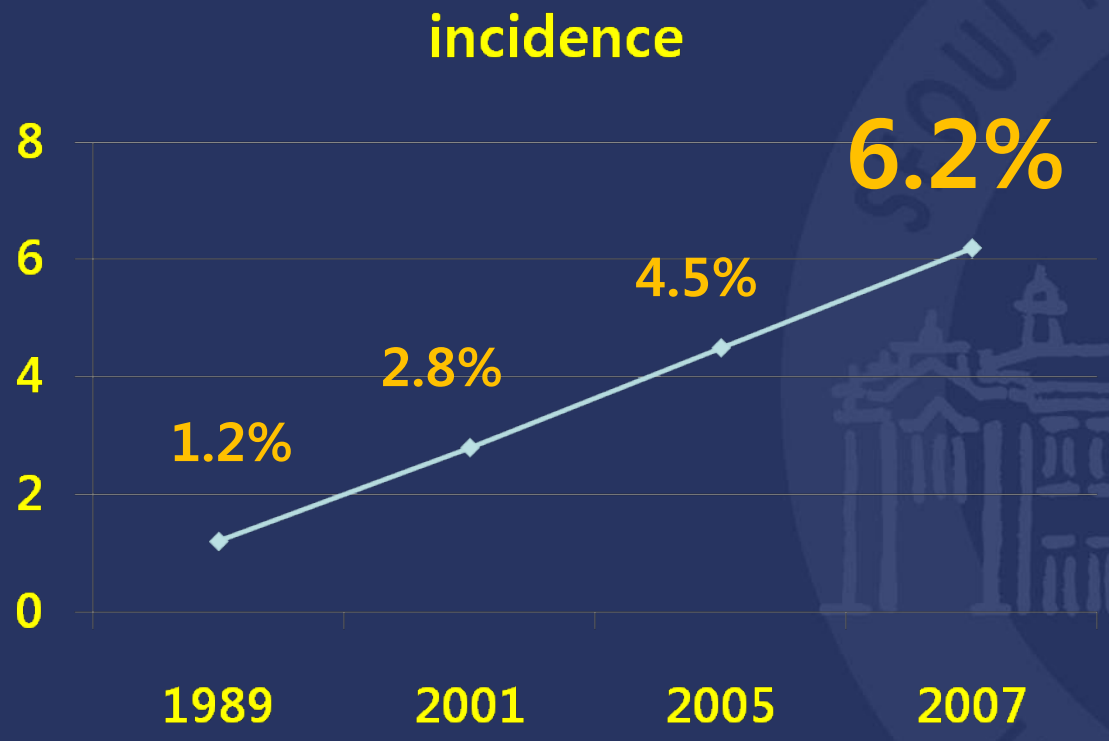
Introduction

Prostate Cancer In Korea

- PCa accounts for 6.2% of male cancer
- Rapidly increasing in Korean men



Prostate cancer: 5th prevalent cancer among Korean men

(2009 Korean Ministry of Health & Welfare)

Detection of PCa – PSA era

- Newly diagnosed PCa
  - Localized PCa↑, Locally advanced PCa↓
  - Overdiagnosis : as high as **56%**

    (Etzioni R, et al. 2002, J Natl Cancer Inst)

    (Johansson JE, et al. 2004, JAMA)
  - Stage migration

Introduction

Detection of PCa –PSA era : Lead time bias

- Stage migration + PSA screening

  → **Lead time bias**

  – Diagnosis before clinically evident

  – **12.3yr (at age 55)**

  (ERSPC ; European Randomised Study of Screening for Prostate Cancer)

  (Draisma et al, 2003, J Natl Cancer Inst)

Introduction

All prostate Cancer needs treatment ?

- Autopsy study
  - 50% of men in 40-49yr harbour PCa. (Sakr WA et al, 1994, autopsy study of 249cases)
  - 21% of men in >50yr (Yatani R , 1982, Int J Cancer)
  - 67% of men in >80yr (Rullis I, 1975, Urology)

- Until death, ongoing PCa without problem.

→ **Clinically insignificant PCa ?**

Introduction

Clinically Insignificant Prostate Cancer

Unsettled Issue

Potential Benefits

Potential Harms

- Ongoing controversy on management

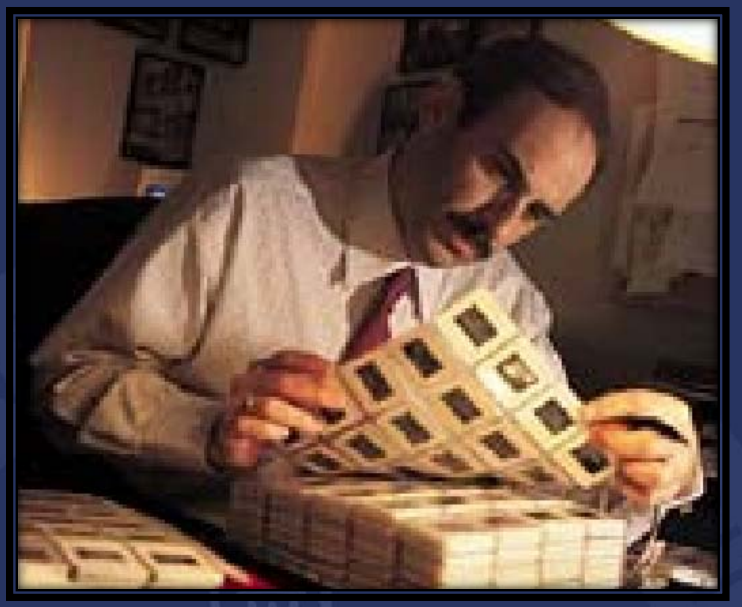
What is CIPC?

Epstein criteria

- Epstein criteria

  (Dr. Jonathan Epstein)

  - To predict
  - Clinically insignificant PCa (CIPC)



- Pathological insignificant PCa

(tumor vol<0.2cm^3, pGS ≤6 and Organ-confined)

most widely used definition
for clinically insignificant prostate cancer (CIPC).

Epstein criteria

- Clinical stage T1c
- PSA density <0.15ng/ml
- No Gleason pattern 4 or 5
- Fewer than 3 positive cores (From 6 cores)
- <50% cancer per core

Predict the presence of insignificant tumour

Epstein JI, et al. JAMA, 1994

Definition of insignificant or low-risk PCa

D'Amico	PSA ≤10	No GS 4 or 5	Cstage T2a or ↓		
Dall'Era	PSA ≤10	No GS 4 or 5	Cstage T2a or ↓	PSAD <0.15	<33% (+)cores
Patel		GS ≤ 7	Cstage T3 or ↓		
Soloway	PSA < 15	No GS 4 or 5	Cstage T2 or ↓		<50% (+)cores
Van den Bergh	PSA < 10	No GS 4 or 5	Cstage T1c-T2b	PSAD <0.20	3 (+) core ↓
Van As	PSA < 15	GS ≤ 7(3+4)	Cstage T1-T2a		<50% (+)cores
Dall'Era	PSA <10 and stable	No GS 4 or 5 GS sum 6		≤50% single	≤33% (+)cores

Bastian et al. Eur Urol, 2009

Epstein criteria

- Validation study of Epstein criteria
  - **94%** accuracy to pathologically insignificant PCa.

(Epstein JI, et al. J Urol, **1998**)

- Contemporary update in USA (by Bastian et al)
  - 237 T1c – nonpalpable pts with RP
  - Accuracy : **84%**
  - Organ confined accuracy : **91.6%**

Characteristics of Insignificant Clinical T1c Prostate Tumors

A Contemporary Analysis

CANCER November 1, 2004 / Volume 101 / Number 9

Epstein criteria

Really accurate ?
- safe for Active Surveillance ?

- Validation of Epstein criteria **recently~**
  - European Men
  - Middle east Men
  - Korean Men

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

Eur Urol 2008

European Association of Urology

Prostate Cancer

Validation of the Contemporary Epstein Criteria for Insignificant Prostate Cancer in European Men

Claudio Jeldres[a,1], Nazareno Suardi[a,1], Jochen Walz[a,b], Georg C. Hutterer[a,c], Sascha Ahyai[b], Jean-Baptiste Lattouf[a], Alexander Haese[b], Markus Graefen[d], Andreas Erbersdobler[e], Hans Heinzer[d], Hartwig Huland[b,d], Pierre I. Karakiewicz[a,*]

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- Between 1996 and 2006
- 2580 men underwent RP
  - 366 fulfilled the contemporary epstein criteria
  - Analysis : **pathologically unfavorable PCa**.

Validation in European Men

- pGleason 7–10
  - **88 patients (88/366 , 24%)**
  - 30 (34.1%) of the 88 patients

  → Non–organ-confined disease (30/366. 8.3%)

- Epstein criteria – **Underestimation !**
- : inaccurate in 24% of patients

Accuracy : 76%

Int Urol Nephrol
DOI 10.1007/s11255-009-9670-6

UROLOGY - ORIGINAL PAPER

Validation of Epstein criteria of insignificant prostate cancer in Middle East patients

Ihab A. Hekal · Nasr A. El-Tabey · Mohamed Adel Nabeeh · Ahmed El-Assmy · Mohamed Abd El-Hameed · Adel Nabeeh · Elhousseiny I. Ibrahiem

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- On past 8 years
- 35 in Epstein criteria (70 T1c)
  - **16 (45.7%) GS ≥7**
  - 3 (8.6%) Non-organ confined
  - 14 (40%) upgrading

Accuracy : 54.3%

In Koreans ?

2010

BJUI
BJU INTERNATIONAL

Application of the Epstein criteria for prediction of clinically insignificant prostate cancer in Korean men

Sang E. Lee, Dae S. Kim, Won K. Lee, Hong Z. Park, Chang J. Lee, Seung H. Doo, Seong J. Jeong, Cheol Y. Yoon, Seok-Soo Byun, Gheeyoung Choe*, Sung I. Hwang†, Hak J. Lee† and Sung K. Hong

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Accepted for publication 12 August 2009

Study Type – Prognosis (case series)
Level of Evidence 4

OBJECTIVE

To investigate the rate of pathologically confirmed unfavourable prostate cancers among Korean men who fulfilled the contemporary Epstein criteria for clinically insignificant prostate cancer.

PATIENTS AND METHODS

This was a retrospective study of 131 Korean men who underwent radical prostatectomy (RP) for clinically insignificant prostate cancer as defined by contemporary Epstein criteria. We assessed the percentage of unfavourable prostate cancer (pathological Gleason sum ≥7 and/or extraprostatic extension [EPE]) among these men and tried to identify useful predictors for such unfavourable tumour profiles using uni- and multivariate analyses.

RESULTS

Among 131 men with clinically insignificant prostate cancer, 40 (30.5%) had pathological Gleason ≥7 tumours after RP. Of these 40 men, four (3.1%) also had EPE on examination of RP specimen. All those who did not have Gleason score upgrading after RP had organ-confined disease from examination of RP specimen. Overall, 40 (30.5%) of the 131 men who fulfilled the contemporary Epstein criteria for clinically insignificant prostate cancer before RP had pathologically unfavourable disease. Among our patients, no significant preoperative predictor of pathologically unfavourable disease was identified using uni- and multivariate analyses.

CONCLUSION

Our results showed that a significant proportion of contemporary Korean patients who meet all the conditions of the contemporary Epstein criteria for prediction of clinically insignificant prostate cancer might actually harbour prostate cancer with unfavourable pathological features. Such findings should be considered when treatment options are contemplated based upon the Epstein criteria among Asian patients.

KEYWORDS

insignificant prostate cancer, Epstein criteria, Korea

Materials and Methods

- Jan. 2004 ~ April 2009
- 1011 men underwent radical prostatectomy for PCa

- Exclusion criteria (n=311)
  - Neoadjuvant therapy
  - Prostate biopsy at other institutions
  - Prostate biopsy with <12 cores obtained

- Definition of contemporary Epstein criteria for CIPC
  - clinical T1c
  - PSA density ≤ 0.15
  - Gleason score ≤ 6
  - Fewer than three biopsies with PCa
  - Up to 50% of cancer involvement in any core

131 men (18.7%) was included in final analysis.

- Definition of unfavorable PCa
  - Pathological Gleason sum 7-10
  - Extraprostatic extension(EPE) of tumor
    - Cancer (≥pT3) with capsular penetration, seminal vesicle involvement, nodal involvement, or a combination of those

Jeldres et al, Eur Urol 2008

Preoperative characteristics of subjects (n=131)

Mean age (yrs)		64.9 (43.0-76.0)
Mean BMI (kg/m^2)		24.7 (18.1-32.9)
Mean preoperative PSA (ng/ml)		4.7 (0.97-12.9)
Mean prostate volume (ml)		47.4 (22.0-114.0)
Mean PSA density		0.1 (0.03-0.15)
No. total biopsy cores obtained (%)	12	84 (64.1)
	≥ 13	47 (35.9)
Biopsy Gleason sore (%)	< 6	2 (1.5)
	6	129 (98.5)
No. positive cores (%)	1	89 (67.9)
	2	42 (32.1)
Mean maximum % of cancer in any core		13.3 (1.3-42.9)

Results

Pathological findings from analyses of RP specimens

Findings	No. patients (%)
Total patients	131 (100)
Non-organ confined tumor	
Extraprostatic extension	4 (3.1)
Seminal vesicle invasion	0 (0)
Lymph node involvement	0 (0)
Pathological Gleason score	
6	91 (69.5)
7 (3+4)	37 (28.2)
7 (4+3)	3 (2.3)
Positive surgical margin	10 (7.6)

Proportion of unfavorable prostate cancer

	Organ-confined Ds.	Non-organ-confined Ds.	Total
GS 6	91 (69.5%)	0 (0%)	91 (69.5%)
GS 7	36 (27.4%)	4 (3.1%)	40 (30.5%)
Total	127 (96.9%)	4 (3.1%)	131 (100%)

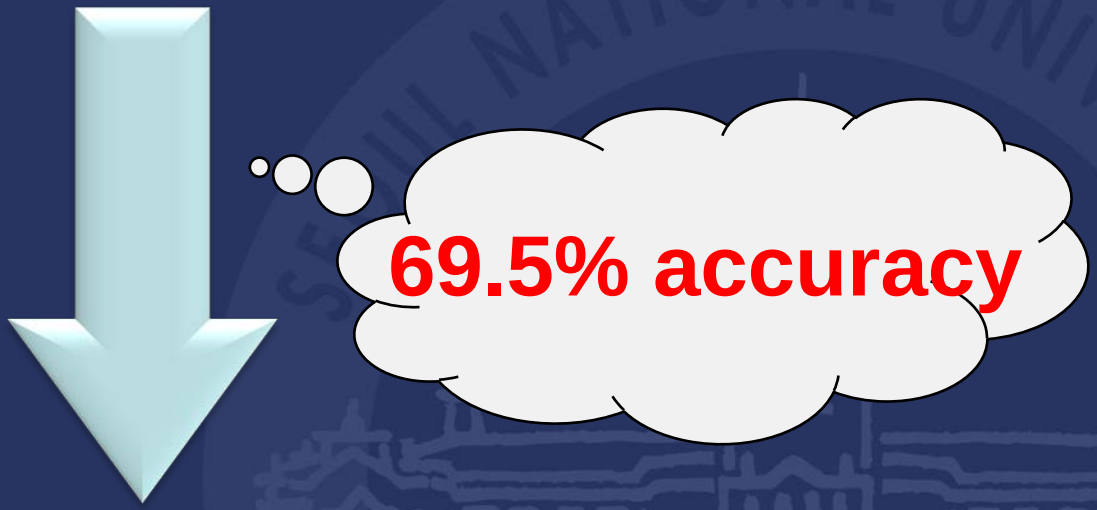
Unfavorable prostate cancer = 40 (30.5%)

69.5% accuracy

(North American : 84%, European : 76%)

Conclusions

Significant proportion (**30.5%**) of contemporary Korean patients who met all the conditions of Epstein criteria



Unfavorable pathological features

World J Urol (2009) 27:271–276
DOI 10.1007/s00345-008-0343-3

ORIGINAL ARTICLE

D'Amico classification

Prediction of Gleason score upgrading in low-risk prostate cancers diagnosed via multi (≥12)-core prostate biopsy

Sung Kyu Hong · Byung Kyu Han · Seung Tae Lee · Sung Soo Kim · Kyung Eun Min · Sung Jin Jeong · Hyeon Jeong · Seok-Soo Byun · Hak Jong Lee · Gheeyoung Choe · Sang Eun Lee

Proportion of Korean patients with **low risk** prostate cancer upgraded to Gleason ≥ 7 after RP

39.9%

BJUI
BJU INTERNATIONAL

Prediction of pathological outcomes for a single microfocal (≤3 mm) Gleason 6 prostate cancer detected via contemporary multicore (≥12) biopsy in men with prostate-specific antigen ≤10 ng/mL

Sung Kyu Hong, Woong Na, Jung Min Park, Seok-Soo Byun, Jong Jin Oh, Jung Soo Nam, Chang Wook Jeong, Gheeyoung Choe*, Hak Jong Lee†, Sung Il Hwang† and Sang Eun Lee

*Department of Urology, *Department of Pathology, and †Department of Radiology, Seoul National University Bundang Hospital, Seongnam, Korea*

In press 2011

- A single microfocal Pca detected on biopsy:
  → often considered to be low risk disease!!!
  → various definitions exist! (***Terris et al***; ≤ 3 mm)

- 119 Korean men with prebiopsy PSA ≤ 10 ng/ml + a single microfocal (≤ 3 mm) Pca on ≥ 12-core biopsy
  → All underwent RP !

- Definition of unfavorable PCa
  - Pathological Gleason sum 7-10
  - Extraprostatic extension(EPE) of tumor
    - Cancer (≥pT3) with capsular penetration, seminal vesicle involvement, nodal involvement, or a combination of those

Overall rate: 24.4%

- Definition of insignificant PCa
  - Pathological Gleason sum ≤ 6
  - Pathologically organ-confined tumor
  - Tumor volume < 0.5 ml

Overall rate: 44.5%

TABLE 2 Univariable and multivariable logistic regression model for prediction of insignificant prostate cancer

Variable	Univariable		Multivariable
	P value; OR	AUC (%)	*P* value; OR
Age	0.31; 0.60	53.6	0.48; 0.69
Body mass index	0.27; 0.66	55.0	0.32; 0.66
Clinical stage	0.54; 0.72	51.9	0.48; 0.65
Prostate-specific antigen	0.45; 0.72	53.1	0.23; 2.16
Prostate-specific antigen density (ng/mL/cm^3) (≥0.15 vs <0.15)	0.07; 0.46	57.8	0.02; 0.23
Prostate volume	0.37; 0.99	50.6	0.07; 0.97
No. of biopsy cores	0.64; 1.20	52.0	0.54; 1.29
% of cancer in positive core	0.10; 0.95	56.2	0.74; 0.94
Tumour length in positive core	0.13; 0.69	55.3	0.79; 1.03
Non-tumour length in positive core	0.37; 1.06	53.1	0.98; 1.03
Area under the curve (%)			68.2

AUC, area under the curve; OR, odds ratio.

TABLE 3 Univariable and multivariable logistic regression model for prediction of unfavourable prostate cancer

Variable	Univariable		Multivariable
	P value; OR	AUC (%)	*P* value; OR
Age	0.11; 0.39	57.5	0.38; 1.85
Body mass index	0.50; 1.34	53.5	0.29; 1.65
Clinical stage	0.49; 1.50	52.5	0.38; 1.75
Prostate-specific antigen	0.03; 2.64	60.1	0.20; 2.38
Prostate-specific antigen density ($ng/mL/cm^3$) (≥0.15 vs <0.15)	0.57; 1.44	51.9	0.77; 1.22
Prostate volume	0.77; 1.00	53.2	0.95; 1.00
No. of biopsy cores (12 vs ≥13)	0.74; 0.86	51.7	0.86; 0.92
% of cancer in positive core	0.89; 1.00	51.0	0.47; 0.87
Tumour length in positive core	0.54; 1.17	53.5	0.40; 2.74
Non-tumour length in positive core	0.29; 1.07	58.7	0.98; 1.00
Area under the curve (%)			66.9

AUC, area under the curve; OR, odds ratio.

Conclusions

- Our data showed that clinical and biopsy-related parameters currently available have **limited value** in the prediction of pathologically insignificant or unfavorable prostate cancer in patients with a single positive core and low PSA level.

- Further efforts should be made to identify more accurate predictors of actual pathological characteristics and/or prognoses of prostate cancers to ultimately enhance the selection of candidates for active surveillance or immediate treatments.

Epstein criteria

Really accurate ?
- Active Surveillance for who ?

- Correctly assessing the risk

Challenging task for Urologist

Criteria for selection of AS

→Too broad or inaccurate?

The Future of Active Surveillance

- Novel biomarker
  - TMPRSS2: ERG : more aggressive phenotype
    (Demichelis F et al. ; Oncogene, 2007)
  - GSTP1 hypermethylation : predictor BCR
    (Bastian PJ et al. ; Clin Cancer Res, 2005)

- Current trial of active surveillance
  - **START trial**
    (Standard Treatment Against Restricted Treatment)
  - 2130 enrol – Canada, US, United Kingdom
  - **PRIAS study**
    (Prostate Cancer Research International: Active Surveillance)
  - Rotterdam section of the ERSPC, Netherlands

Conclusions

- Increasing prostate cancer since PSA era → also in Asia

  Increasing **Insignificant prostate cancer**

- Concern on overdetection, overtreatment:

  → "Need for active surveillance is REAL !!!!, ..but….."

- Current methods for identifying insignificant prostate cancer (selection of candidates for active surveillance) :

  Epstein criteria, other preoperative tools…….

  → ***room for improvement exists*** !!! (**especially for Asians**…)

- Further study is necessary!!!!!

THANK YOU !!!