Progress in Prostate Cancer Grading

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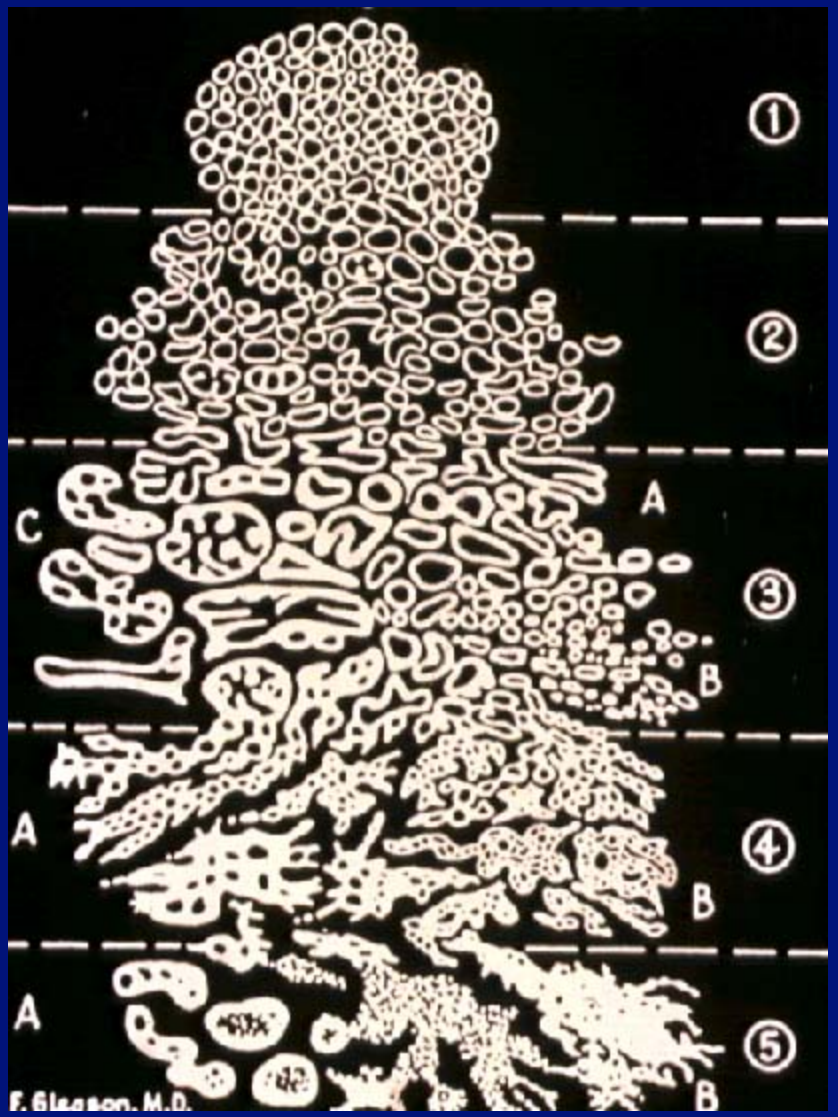
Disclosure:
3DBiopsy - stakeholder

Prostatic Adenocarcinoma

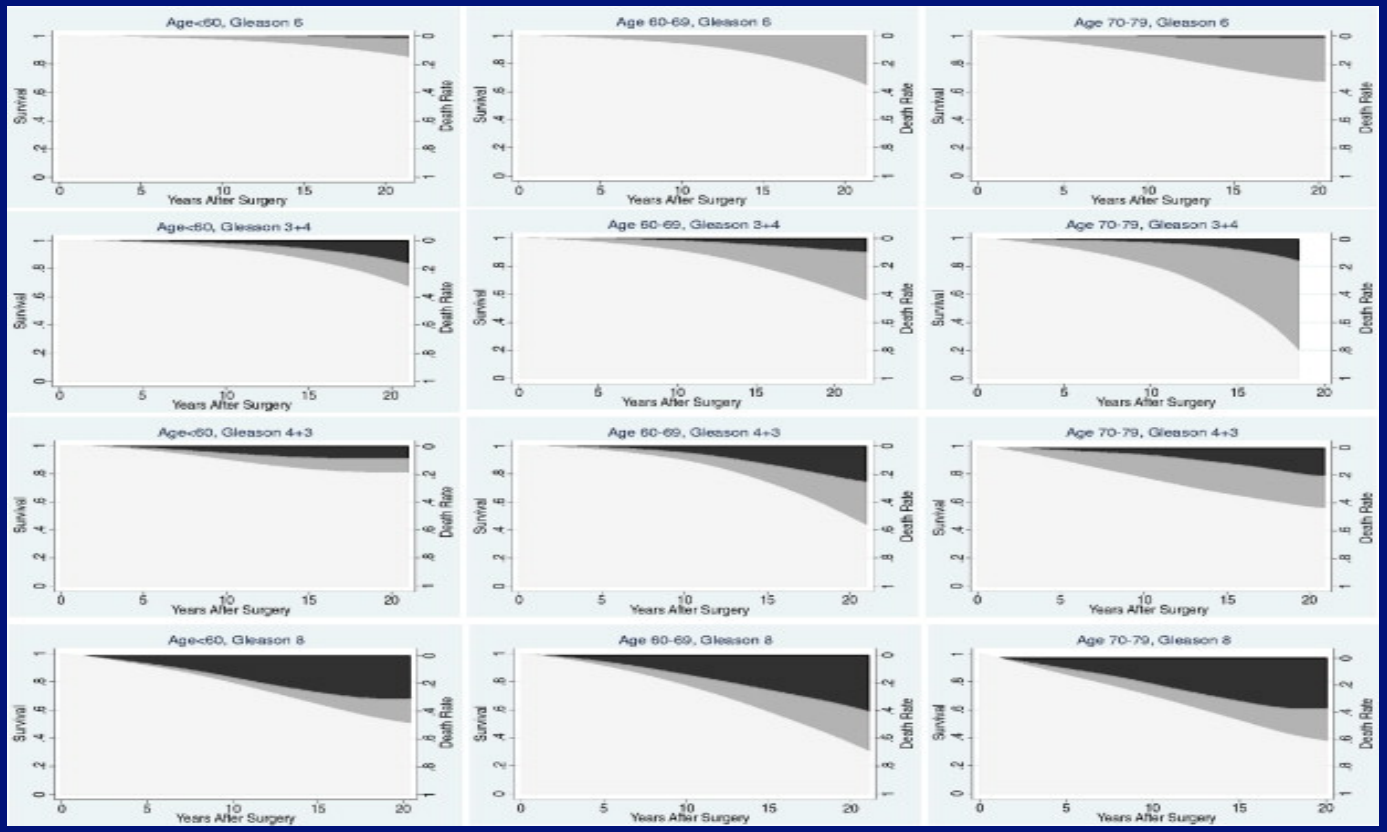
Gleason Grading

- Morphologic resemblance to normal prostate
- Degree of invasiveness
- Score = most + 2nd most
- Refinements:
  - 1970s – validation and expansion of criteria for pattern 4[1]
  - 1992 – subdivision of patterns 3-5[2]



1. Gleason DF. *Urologic Pathology: The Prostate,* 1977.
2. Gleason DF. *Hum Pathol* 1992.

Predicting 15-year prostate cancer specific mortality after radical prostatectomy[1]



PCSM (black areas) and mortality from competing causes (gray areas) by pathological Gleason score and patient age at diagnosis.

N=23,910 across 5 institutions

1. Eggener SE, et al. J Urol 2011;185:869-75. http://dx.doi.org/10.1016/j.juro.2010.10.057

Problems with Gleason System

- Most low grade patterns (1 and 2) now recognized as benign
- Confusion on how to grade cribriform cancers
- Certain variants of cancer not described in Gleason system
- Tumor sampling issues
  - Prostate cancer heterogeneous
  - Small caliber needles for biopsy

2005: ISUP met to address these issues and provide guidelines for grading using the Gleason system

- Based on data and experience

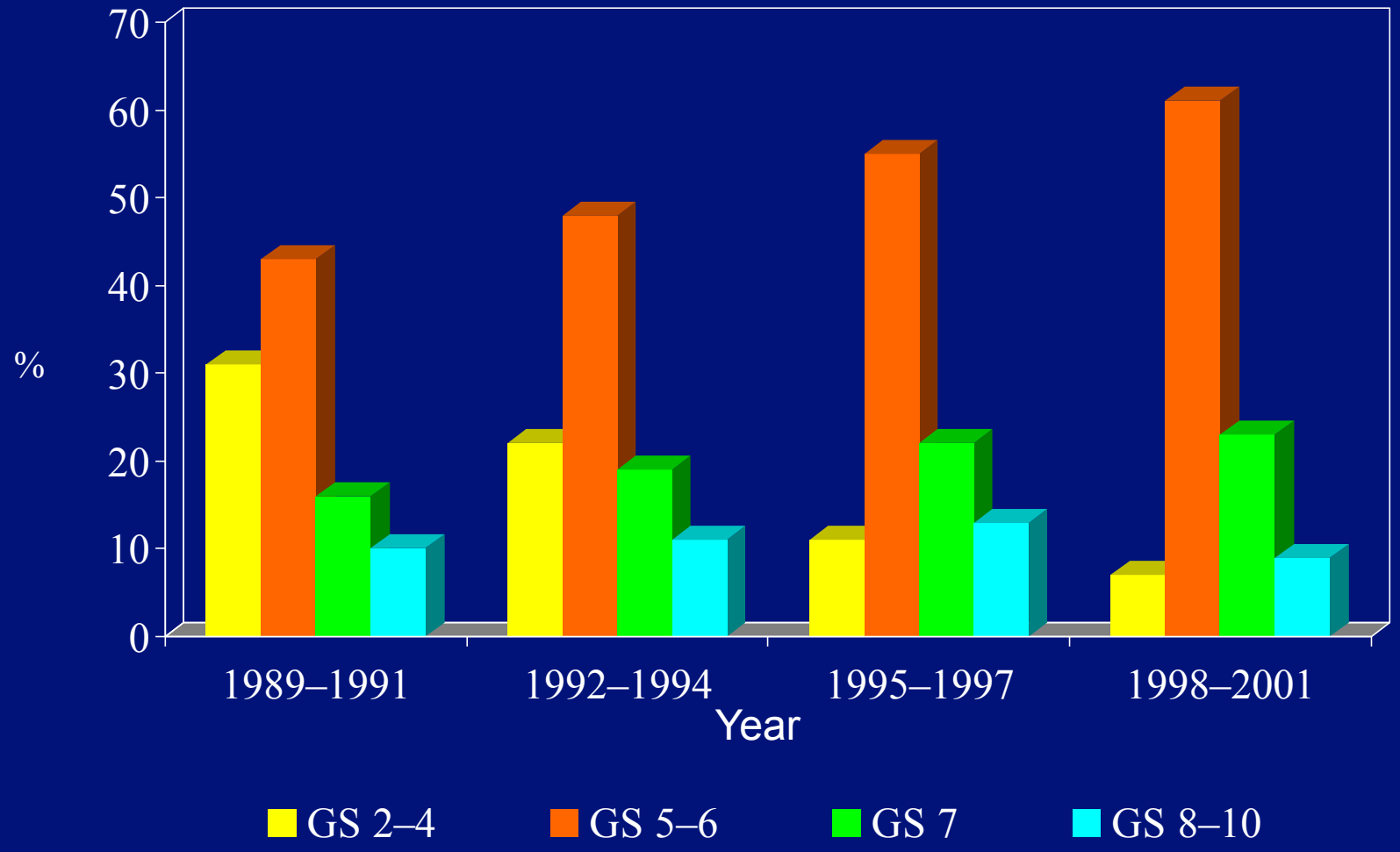
2005 ISUP Gleason Grading Consensus

Recommendations based on grading practices of 80 leading urologic pathologists around the world

- Restrictions on assignment of very low grades (patterns 1 and 2) on biopsies
  - Most cases upgraded on prostatectomy or found to be benign with use of basal cell stains

AJSP 2005;29:1228-1242

Prostate Cancer
Grade at Diagnosis—CaPSURE



GS=Gleason Score

Cooperberg MR, et al. *J Urol* 2003;170:S21-5.

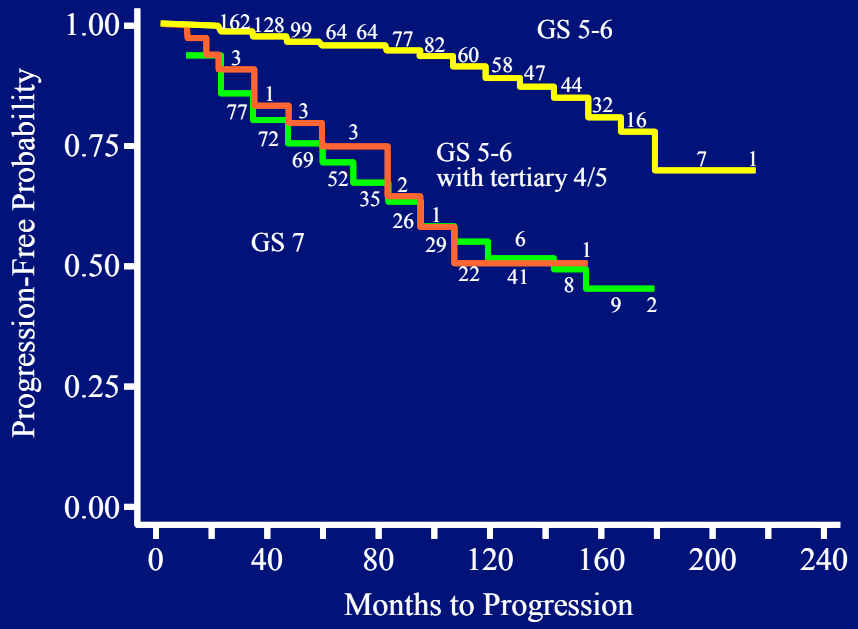
2005 ISUP Gleason Grading Consensus

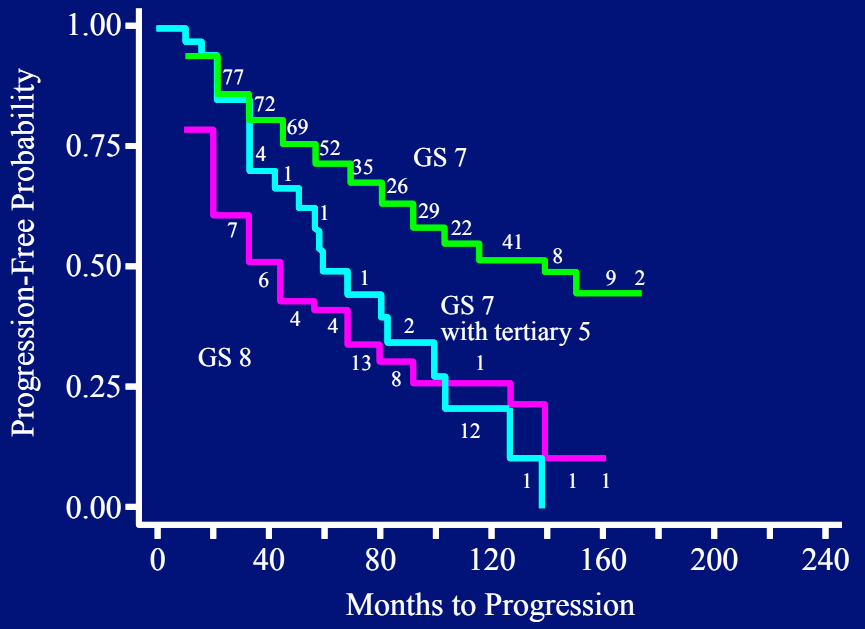
Recommendations based on grading practices of 80 leading urologic pathologists around the world

- Restrictions on assignment of very low grades (patterns 1 and 2) to biopsies
  - Most cases upgraded on prostatectomy or found to be benign with use of basal cell stains
- Guidelines for assigning grade to cribriform patterns of cancer
  - Large or irregular=grade 4 (most cases); small round=grade 3
- Grading histological variants (ex. Ductal Ca=grade 4)
- Grading biopsies: most prevalent pattern + highest remaining grade

AJSP 2005;29:1228-1242

Significance of Tertiary (<5%) HG Gleason Pattern*



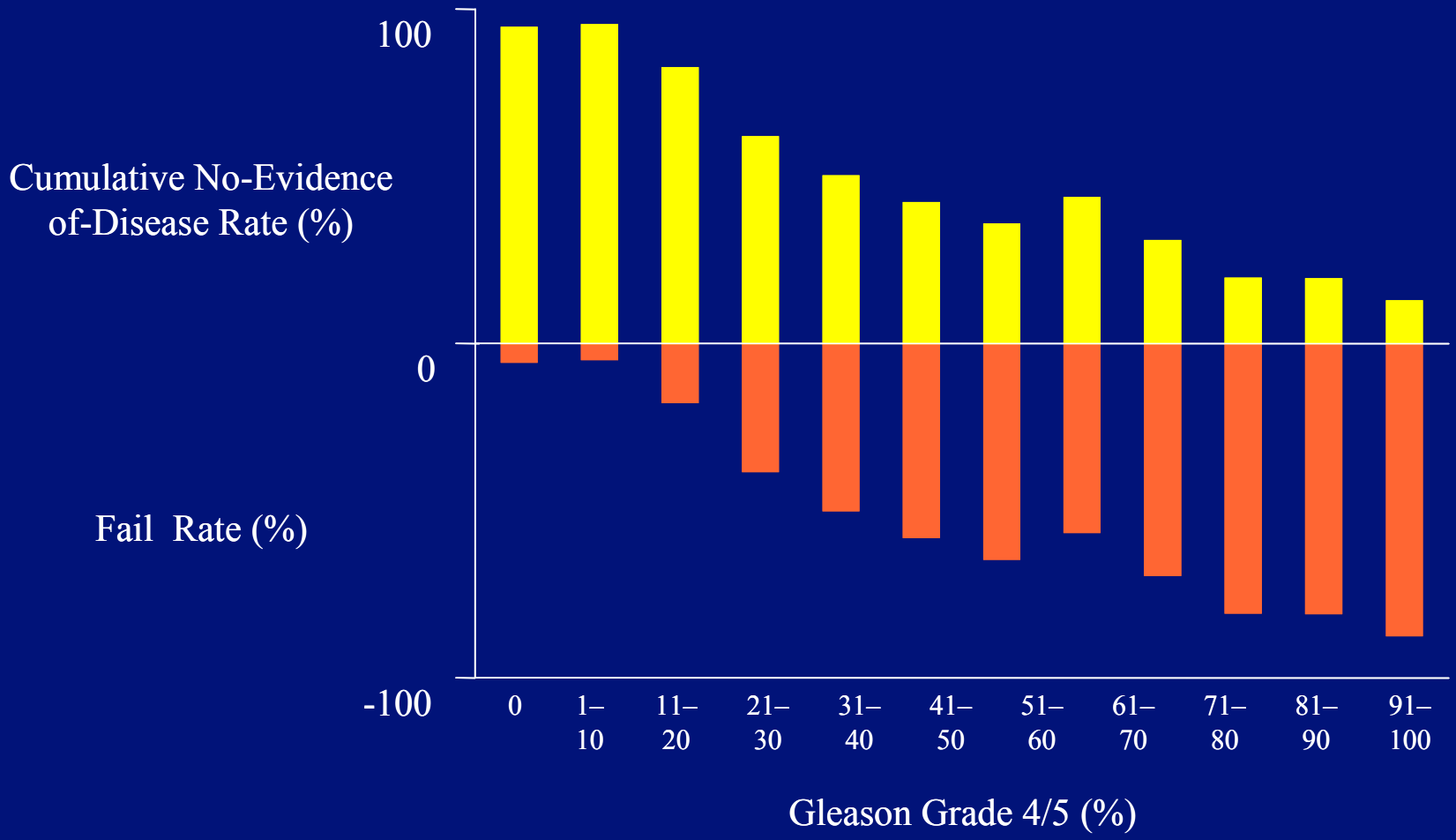


HG = high-grade

*Tertiary pattern is defined as a third Gleason pattern in a tumor that occupies less than 5% of the tumor.

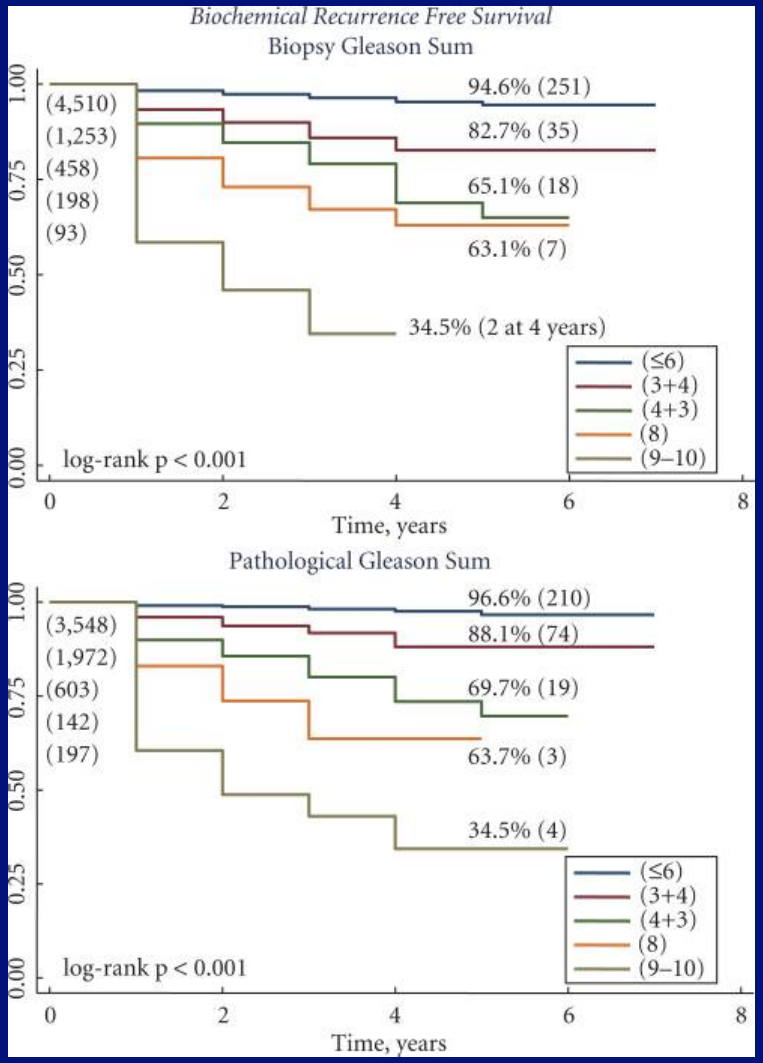
Pan CC, et al. Am J Surg Pathol. 2000;24:563-9.

Failure Rates as a Function of Percent Gleason Pattern 4/5 Cancer



Stamey TA, et al. *JAMA.* 1999;281:1395-400.

Impact of grade* stratification on biochemical recurrence



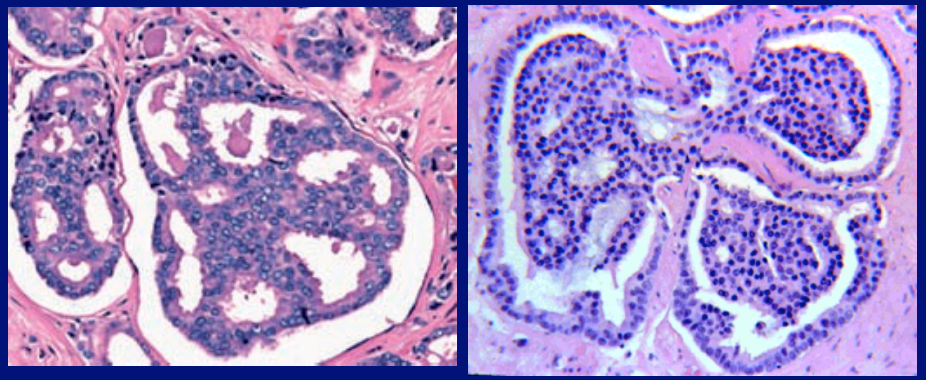
N=7869	Multivariate regression	
	HR (95% CI)	P
Preoperative variables		
Family history	0.77 (0.54-1.08)	0.132
PSA	1.06 (1.04-1.07)	<0.001
cT2b	2.70(1.79-4.06)	<0.001
cT2c-cT3	3.36(1.55-7.31)	0.002
Biopsy Gleason score		
3 + 4	2.19 (1.35-3.56)	0.002
4 + 3	5.38 (3.33-8.68)	<0.001
8	6.92 (3.99-11.98)	<0.001
9-10	10.27 (5.29-19.92)	<0.001
>3 cores	0.96 (0.65-1.42)	0.834
>50% positive	1.99 (1.31-3.00)	0.001

*Tumors graded using 2005 modified Gleason grading criteria

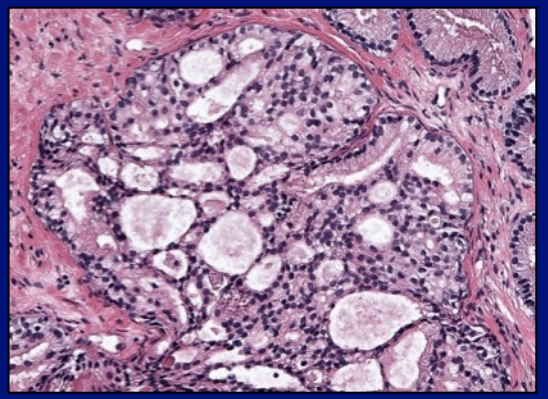
Pierorazio PM et al. BJU Int 2013;111:753-60.
 doi:10.1111/j.1464-410X.2012.11611.x

2014 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma

- 85 GU pathologists and 17 clinicians (urol, med oncol, rad oncol) from 17 countries
- Issues left unaddressed in 2005 or needing reconsideration due to new data
  - Clarification on classification of morphologic patterns
  - Grading of cribriform and glomeruloid patterns as pattern 4



"Small" cribriform and glomeruloid 2005 ISUP pattern 3



"Large" cribriform 2005 ISUP pattern 4

Cribriform cancer highly associated with biochemical recurrence in men treated with prostatectomy

Presence of Nine Histologic Prostate Cancer Patterns and Their Association With PSA Failure in 153 Cases*

Pattern	Present	PSA Failure (n = 76)	Non-PSA Failure (n = 77)	*P* (χ^2)	OR for PSA Failure	95% CI	*P* for OR
Low-grade (S, B, U, and M)	All, 151 (98.7) S, 151 (98.7) B, 78 (51.0) U, 122 (79.7) M, 9 (5.9)	75 (99)	76 (99)	.754†	0.314	0.018-5.464	.427
Fused small	128 (83.7)	68 (89)	60 (78)	053	1.403	0.499-3.945	521
Papillary	80 (52.3)	50 (66)	30 (39)	0009	2.155	0.999-4.645	050
Individual	35 (22.9)	25 (33)	10 (13)	003	2.654	1.069-6.589	035
All cribriform	58 (37.9)	46 (61)	12 (16)	< 0001	5.891	2.534-13.698	< 0001
Any large	58 (37.9)	46 (61)	12 (16)	< 0001	5.583	2.416-12.901	< 0001
Any small	26 (17.0)	21 (28)	5 (6)	0005	6.062	1.931-19.037	002
Large acinar‡	17 (11.1)	15 (20)	2 (3)	0007	10.806	2.152-54.256	004

B, luminal, blue mucin–containing, single, separate acini; CI, confidence interval; M, mucinous/colloid carcinoma without fusion or individual cells; OR, odds ratio; PSA, prostate-specific antigen; S, single, small separate acini; U, undulating, branched, or angulated larger acini that are not truly papillary—no bridging or stromal cores.

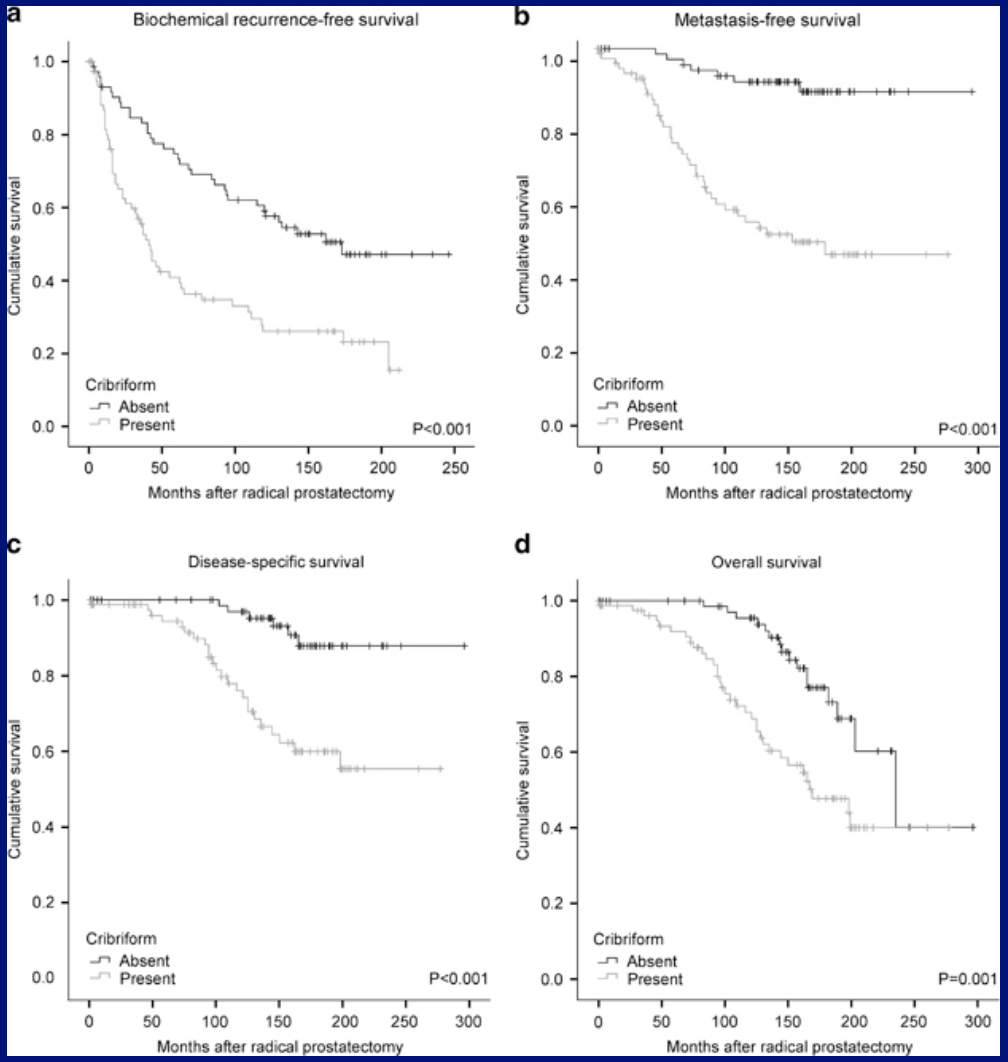
* Data are given as number (percentage) unless otherwise indicated. ORs were determined by multivariate analysis adjusting for the effects of stage, age, margin status, total cancer area, and prostate volume. The F pattern is fused small acini; papillary, true papillary with stromal cores or bridging across acinar spaces; individual, individual cells; small cribriform, rounded acinar spaces with ≤12 lumens and no solid area; and large cribriform, with more sprawling, cribriform to focally solid formations.

† This value derived from the Fisher exact test.

‡ More than one third of cancer volume is composed of large acinar (papillary + cribriform) patterns.

Iczkowski KA, et al. Digital quantification of five high-grade prostate cancer patterns, including the cribriform pattern, and their association with adverse outcome. *Am J Clin Pathol* 2011;136:98-107.

Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer[1]



Adjusted HR = 8.0 (3.0-21), $p<0.001$

Adjusted HR = 5.4 (2.0-15), $p=0.001$

N=161

1. Kweldam CF et al. *Modern Pathol* 2015;28:457-64.

2014 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma

- 85 GU pathologists and 17 clinicians (urol, med oncol, rad oncol) from 17 countries
- Issues left unaddressed in 2005 or needing reconsideration due to new data
  - Clarification on classification of morphologic patterns
  - Grading of cribriform and glomeruloid patterns as pattern 4
  - Adoption of new prognostic grade classification based upon Gleason patterns

Prostate Cancer in the Contemporary Era: Does it make sense to continue to use a 2-10 scaled grading system?

- Gleason score 6 has favorable outcomes
- Gleason score 6 (low grade) is halfway between Gleason score 2 and 10
  - Contributes to reluctance to choose active surveillance
- Gleason scores 2-5 rarely used and not prognostically different from GS6
- Amount of pattern 4/5 most important for prognosis
- Need for a grading system that will distinguish between those that could benefit from AS and those requiring immediate treatment

Classification of Prostate Cancer Using 5-teired Prognostic Grade Groupings

The overall Gleason score is based on the core with the highest Gleason score. Gleason scores can be grouped and range from Prognostic Grade Group I (most favorable) to Prognostic Grade Group V (least favorable).	
Gleason score ≤ 6:	**Prognostic Grade Group I**
Gleason score 3 + 4 = 7:	**Prognostic Grade Group II**
Gleason score 4 + 3 = 7:	**Prognostic Grade Group III**
Gleason score 8:	**Prognostic Grade Group IV**
Gleason score 9-10:	**Prognostic Grade Group V**

- 2014 ISUP (Nov. 2014, Chicago)
  - Voted to adopt 5-teired system (90% consensus)
  - Recommended that percent high grade patterns be specified for groups II and III
  - All modifications to Gleason system should be used in classification

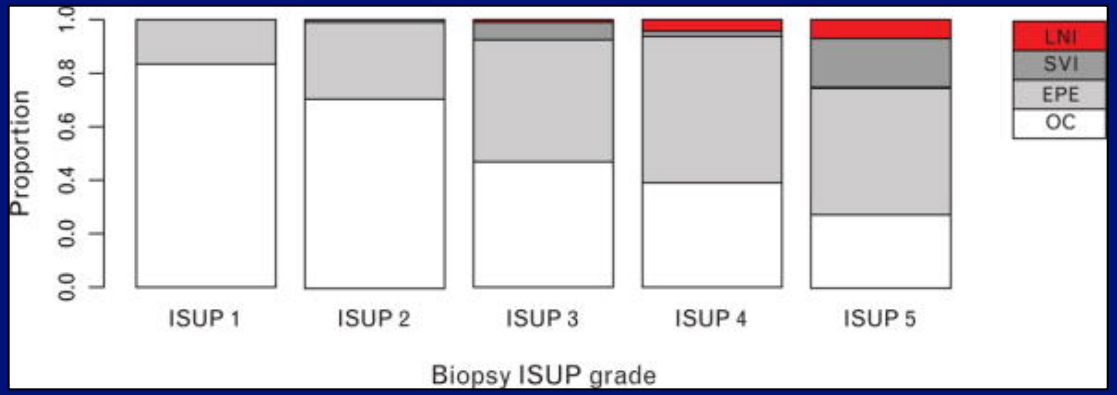
Epstein JI, et al. Am J Surg Pathol 2015;Oct 21

The prognostic significance of the 2014 International Society of Urological Pathology (ISUP) grading system for prostate cancer[1]

Term	Coef	Hazards ratio	SE (coef)	Z	*p* value
Age	−0.00217	0.998	0.0157	−0.139	0.9
PSA	0.03591	1.0	0.0140	2.564	0.01
1	–	1.0	–	–	–
2	0.54761	1.7	0.5338	1.026	0.3
3	1.39397	4	0.5432	2.566	0.01
4	1.92436	6.9	0.6318	3.046	0.002
5	2.40274	11.1	0.5335	4.503	0.000007

Coef, coefficient; PSA, prostate specific antigen; SE, standard error.

Cox proportional hazards regression: patient age, serum prostate specific antigen at presentation and needle biopsy 2014 ISUP grade versus biochemical recurrence-free interval



Proportion of tumours that are organ confined (OC), or show extraprostatic extension (EPE), seminal vesical invasion (SVI) or lymph node involvement (LNI) for cases divided according to ISUP grade of needle biopsy.

Samaratunga, et al. *Pathology* 2015;47:515-519.
DOI: 10.1097/PAT.0000000000000315

Validation of International Society of Urological Pathology (ISUP) grading for prostatic adenocarcinoma in thin core biopsies using TROG 03.04 'RADAR' trial clinical data[1]

Endpoint									
	Distant progression-free survival			**PSA progression-free survival**			**Prostate cancer-specific survival**		
2014 ISUP	Survival (%)*	HR (95% CI)	*p*	Survival (%)*	HR (95% CI)	*p*	Survival (%)*	HR (95% CI)	*p*
1	100	--		88.8	0.63 (0.14-2.77)	0.54	100	--	
2	97.3	1		87.9	1		100	1	
3	81.6	7.27 (2.22-23.73)	0.001	61.2	2.95 (1.74-5.01)	<0.001	94.6	6.92 (0.90-53.39)	0.06
4	83.7	6.63 (1.90-23.16)	0.003	62.9	2.50 (1.39-4.53)	0.002	93.9	7.77 (0.93-64.64)	0.058
5	66.4	15.34 (4.61-51.00)	<0.001	42.0	5/67 (3.22-9.98)	<0.001	79.0	31.07 (4.16-232.2)	0.001

* Unadjusted survival probability at 7 years

1. Delahunt B, et al. Pathology ()ctober 2015) 47(6):520-5.

Validation of International Society of Urological Pathology (ISUP) grading for prostatic adenocarcinoma in thin core biopsies using TROG 03.04 'RADAR' trial clinical data[1]

	C-index (95% CI)		
Endpoint	2005 MGS	2014 ISUP	*p*
Distant PFS	0.709 (0.650-0.767)	0.748 (0.696-0.799)	0.013
PSA PFS	0.701 (0.661-0.741)	0.724 (0.686-0.761)	0.048
PCS survival	0.750 (0.667-0.833)	0.782 (0.714-0.850)	0.001

* PFS=progression-free survival; MGS=Modified Gleason Score

1. Delahunt B, et al. Pathology ()ctober 2015) 47(6):520-5.

Genomic Correlates to the Newly Proposed Grading Prognostic Groups for Prostate Cancer[1]

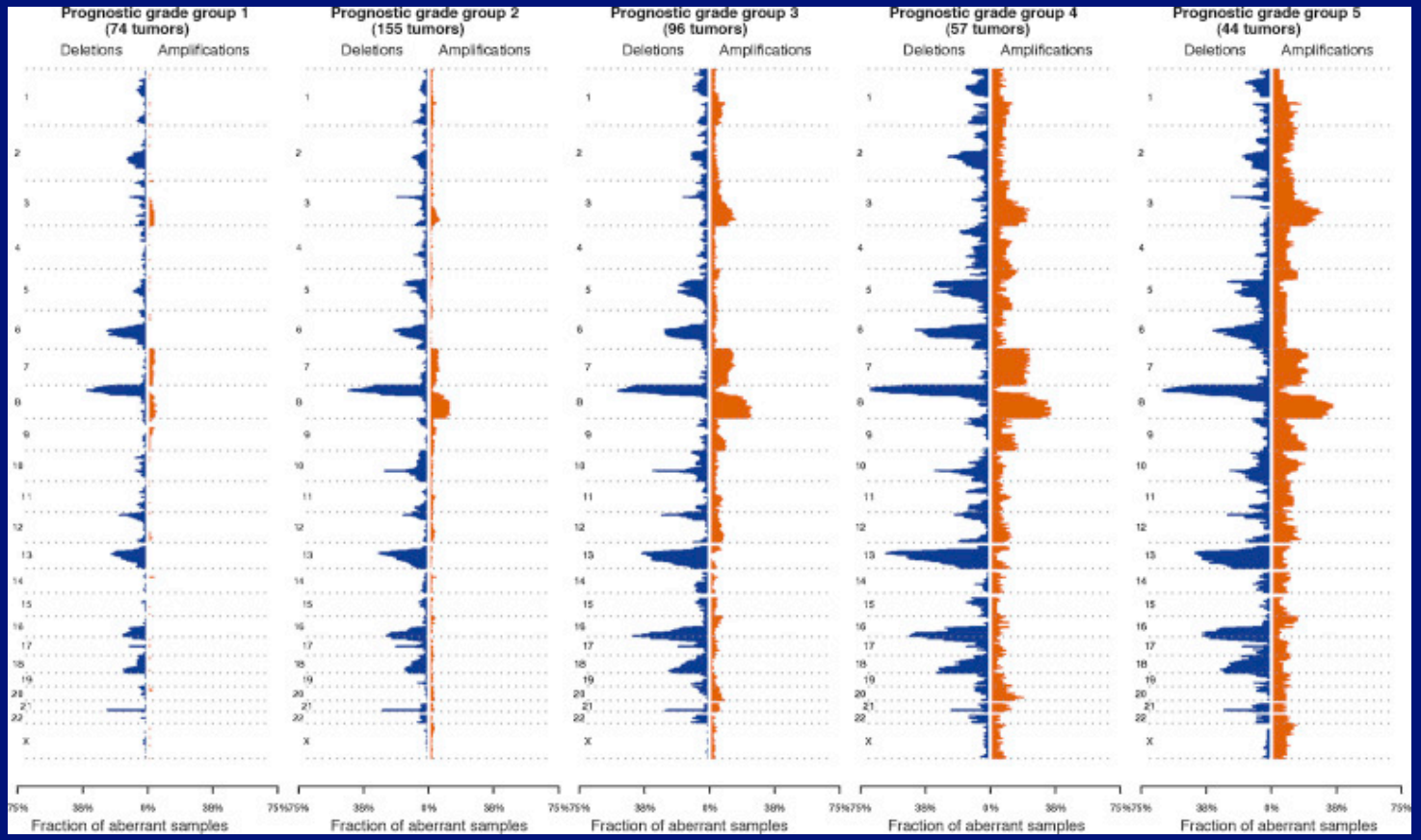


Fig. 1. Landscape of somatic copy number alterations from 426 prostate cancer cases ordered by prognostic grading group from 1 (low) to 5 (high). Blue denotes deletions; red denotes amplifications.

1. Rubin MA, Girelli G, Demichelis F. *Eur Urol* 2015. http://dx.doi.org/10.1016/j.eururo.2015.10.040

Conclusions

- Cancer grade is a strong indicator of prognosis
- The grading system for prostate cancer must be able to distinguish tumors requiring immediate treatment from those that could be candidates for AS
- The Gleason grading system has undergone many refinements to improve predictive accuracy
- The 5-tier Prognostic Grade Groupings proposed by the 2014 ISUP offer excellent prognostic stratification
  - Based on Gleason system
  - Easily understandable
  - Validation studies have confirmed clinical utility