Progress in Prostate Cancer Grading

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Disclosure:
3DBiopsy - stakeholder

Cancer "Grading"

- Phenotypic expression of tumor's biologic aggressiveness
- Reflects the degree to which cancer cells deviate from normal
  - Cell-cell interactions
  - Invasiveness
  - Morphology
- Directly proportional to risk of metastasis

Grading Prostate Cancer

- Cytologic/ nuclear
  - Gaeta/ NPCP
  - Bocking
  - Mostofi
- Archectural
  - MD Anderson
  - Gleason
    - Based on 270 patients (*Cancer Chemother Rep* 1966)

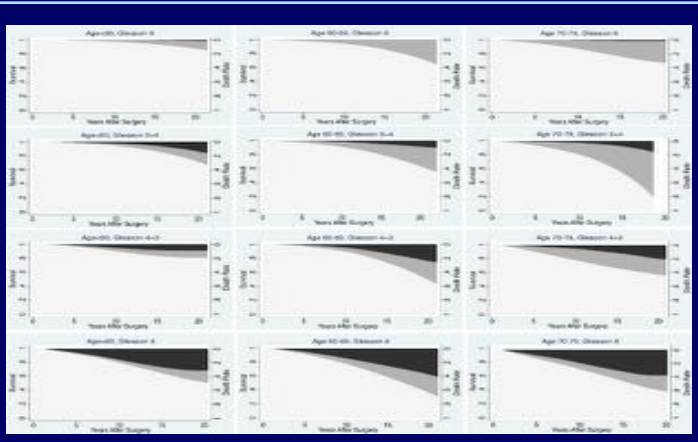
Prostatic Adenocarcinoma

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

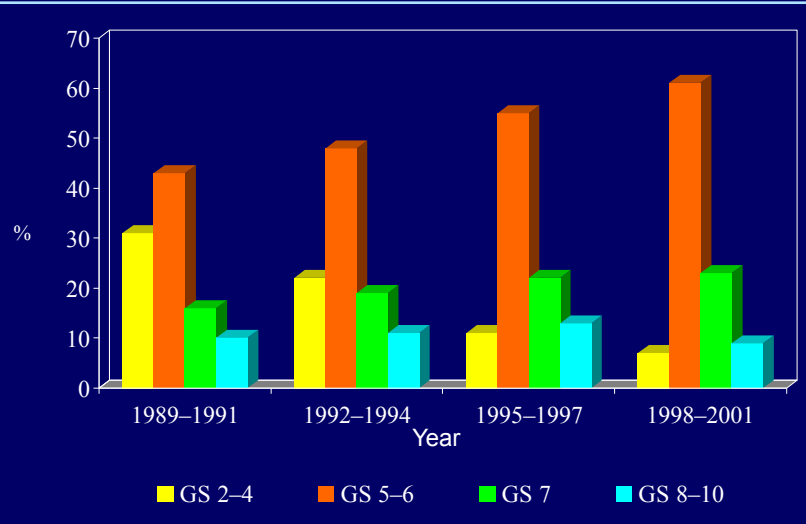
2005 ISUP Gleason Grading Consensus

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 with minor amounts of high grade

AJSP 2005;29:1228-1242

ISUP: Gleason Grading of Minor Secondary/Tertiary Patterns (<5%)

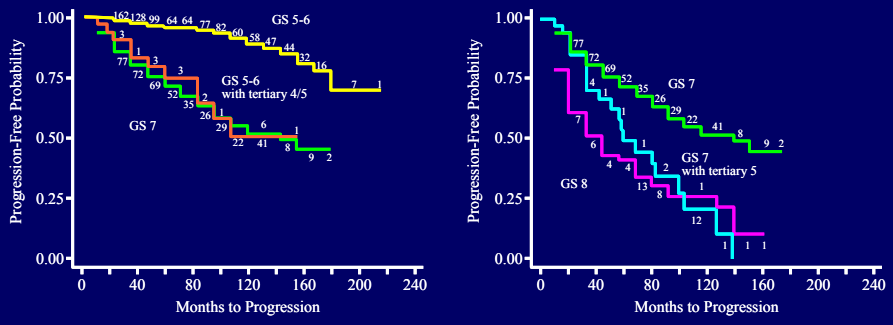
- A minor 2° component of *higher* grade should be reported in Gleason score

  e.g. >95% 3 and <5% 4; score = 7
- A minor 2° component of *lower* grade should *not* be reported in Gleason score

  e.g. >95% 4 and <5% 3; score = 8
- If worst grade is not predominant or secondary grade, generate Gleason score by using predominant and *worst* grade.

  e.g. 70% 3, 25% 4, 5% 5; score = 8 (3+5)

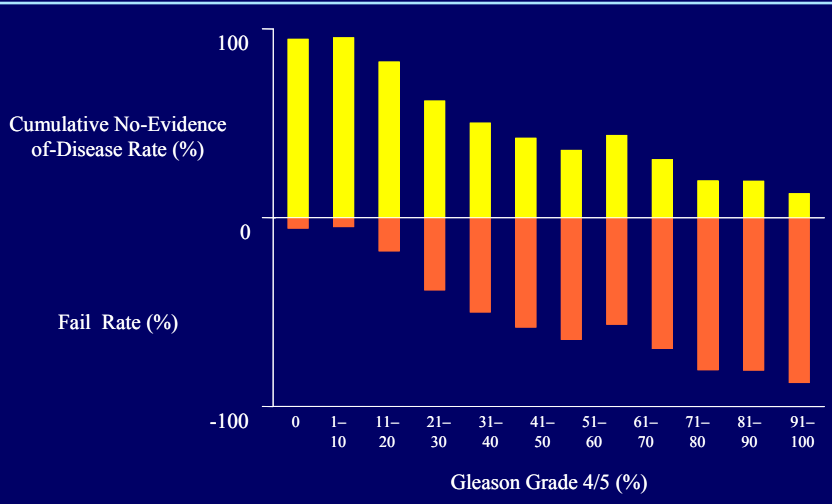
Significance of Tertiary (<5%) HG Gleason Pattern*



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 2005 ISUP Gleason Grading Consensus on biopsy Gleason scores and grade patterns[1]

Distribution of biopsy Gleason scores (GS) before and after ISUP consensus.

	GS≤6	GS=7	GS≥8
2000-2004 (n=908)	617 (68%)	271 (30%)	20 (2%)
2005-2007 (n=423)	232 (55%)	180 (43%)	11 (3%)

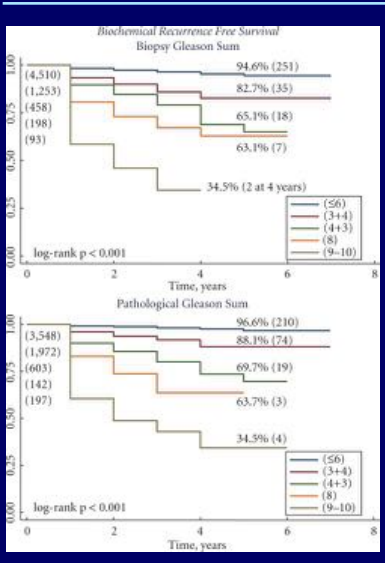
Comparison of mean biopsy Gleason scores and primary (1°) and secondary (2°) Gleason patterns (GP) before and after ISUP consensus.

	2000-2004	2005-2007	P-value*
GS	6.34	6.49	<0.0001
1° GP	3.08	3.10	0.314
2° GP	3.26	3.39	<0.001

* Student's *t-test*

1. Adapted from: Zareba P, et al. Histopathol 2009;55:384-91.

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

Prostate cancer mortality rates according to prostatectomy Gleason score[1]

N=693 patients from 1984-2004

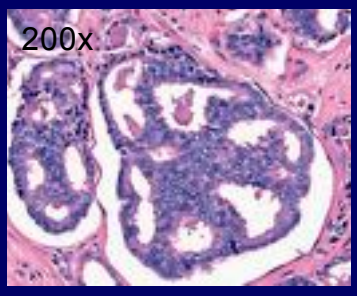
	Standardized Review*				Original Source			
GS	No. of PCa Deaths	Person-Years	No.	Mortality Rate (per 1000 person -years)	No. of PCa Deaths	Person-Years	No.	Mortality Rate (per 1000 person -years)
2-5	0	64.6	6	0	1	2,178.8	171	0.5
6	0	2,216.0	200	0	3	2,331.5	221	1.3
3+4	6	2,864.9	257	2.1	12	1,701.8	171	7.1
4+3	9	1,419.1	134	6.3	9	542.5	55	16.6
8	7	482.3	51	14.5	4	435.3	47	9.2
9-10	15	383.7	45	39.1	8	240.7	28	33.2
Total	37	7,430.6	693	5.0	37	7,430.6	693	5.0

* Using contemporary Gleason grading.

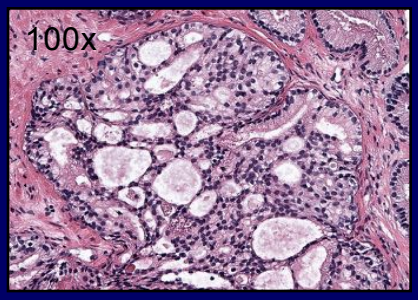
1. Adapted from: Stark JR, et al. *J Clin Oncol* 2009;27:3459-64.

2014 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma

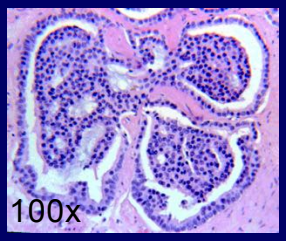
- 85 GU pathologists and 17 clinicians (urol, med oncol, rad oncol) from 17 countries
- Issues left unaddressed in 2005 or needing reconsideration due to new data
  - Clarification on classification of morphologic patterns
  - Grading of cribriform and glomeruloid patterns as pattern 4



"Small" cribriform
2005 ISUP pattern 3



"Large" cribriform
2005 ISUP pattern 4



Glomeruloid
Pattern 3

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.

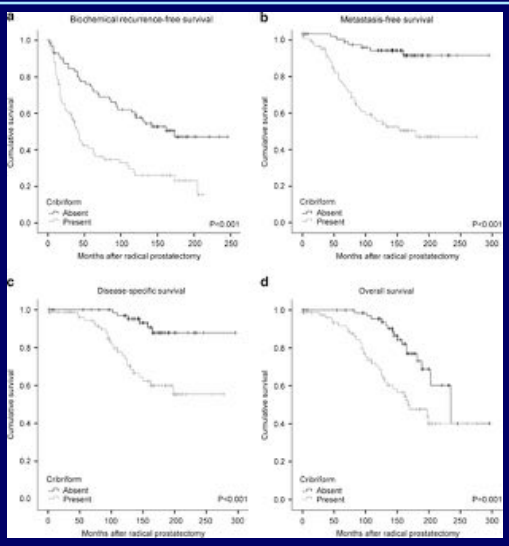
* Data are given as number (percentage) unless otherwise indicated. ORs were determined by multivariate analysis adjusting for the effects of stage, age, margin status, total cancer area, and prostate volume. The F pattern is fused small acini; papillary, true papillary with stromal cores or bridging 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]

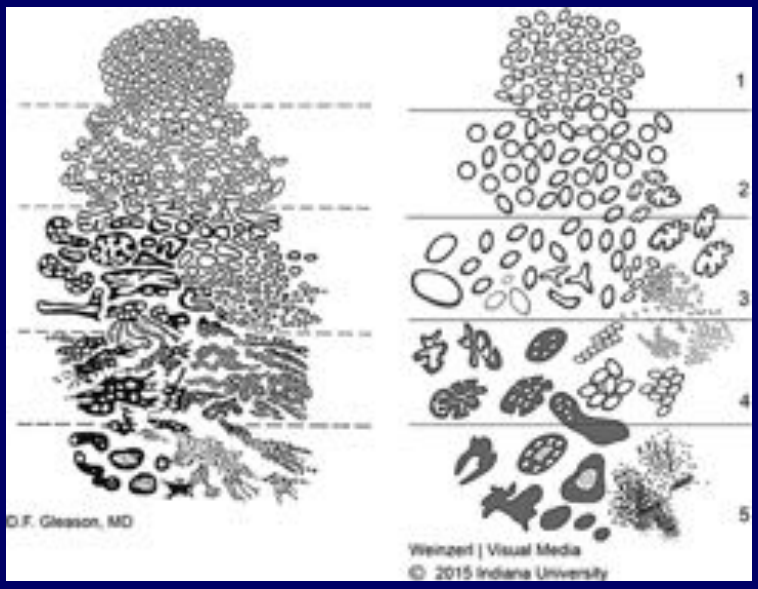


Adjusted HR = 8.0 (3.0-21), p<0.001

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

N=161

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



Human pathol 1992;23:273-9.

ISUP 2015.

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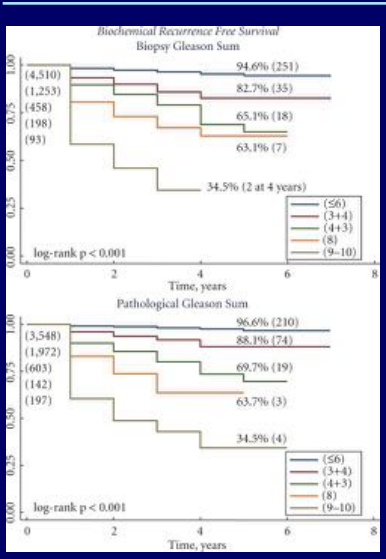
- Issues left unaddressed in 2005 or needing reconsideration due to new data
  - Clarification on classification of morphologic patterns
  - Grading of cribriform and glomeruloid patterns as pattern 4
  - Adoption of new prognostic grade classification based upon Gleason patterns

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

Impact of grade* stratification on biochemical recurrence



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 doi:10.1111/j.1464-410X.2012.11611.x

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**

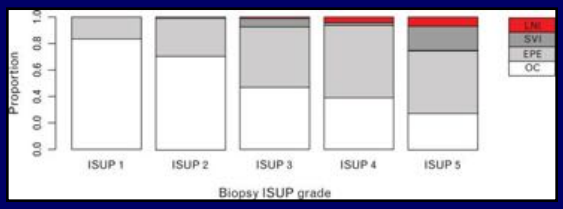
- 2014 ISUP (Nov. 2014, Chicago)
  - Voted to adopt 5-teired system (90% consensus)
  - Recommended that percent high grade patterns be specified for groups II and III
  - All modifications to Gleason system should be used in classification

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.

Wolters Kluwer Health | OvidSP

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	N	Survival (%)*	HR (95% CI)	*p*	Survival (%)*	HR (95% CI)	*p*	Survival (%)*	HR (95% CI)	*p*
1	19	100	--		88.8	0.63 (0.14-2.77)	0.54	100	--	
2	118	97.3	1		87.9	1		100	1	
3	192	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	88	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	79	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 (October 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]

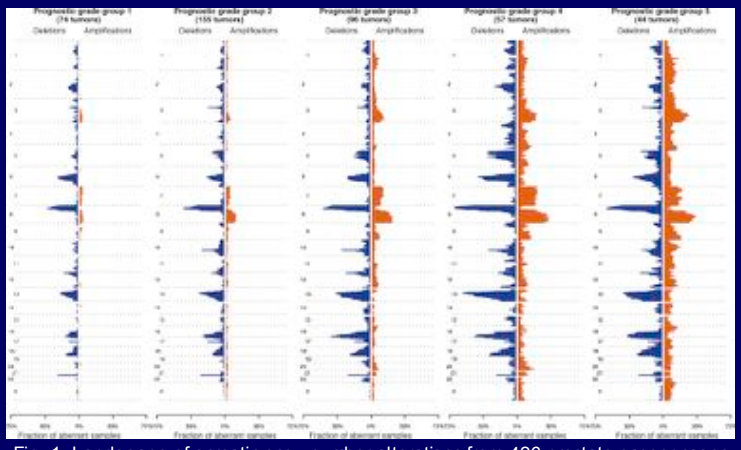


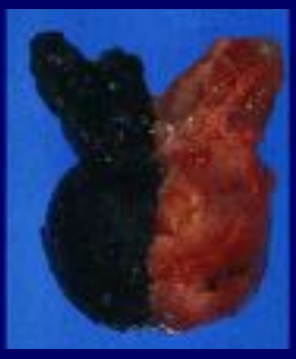
Fig. 1. Landscape of somatic copy number alterations from 426 prostate cancer cases ordered by prognostic grading group from 1 (low) to 5 (high). Blue denotes deletions; red denotes amplifications.

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

Summary

- 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

Can routine biopsy reliably identify tumors that are appropriate for active surveillance?

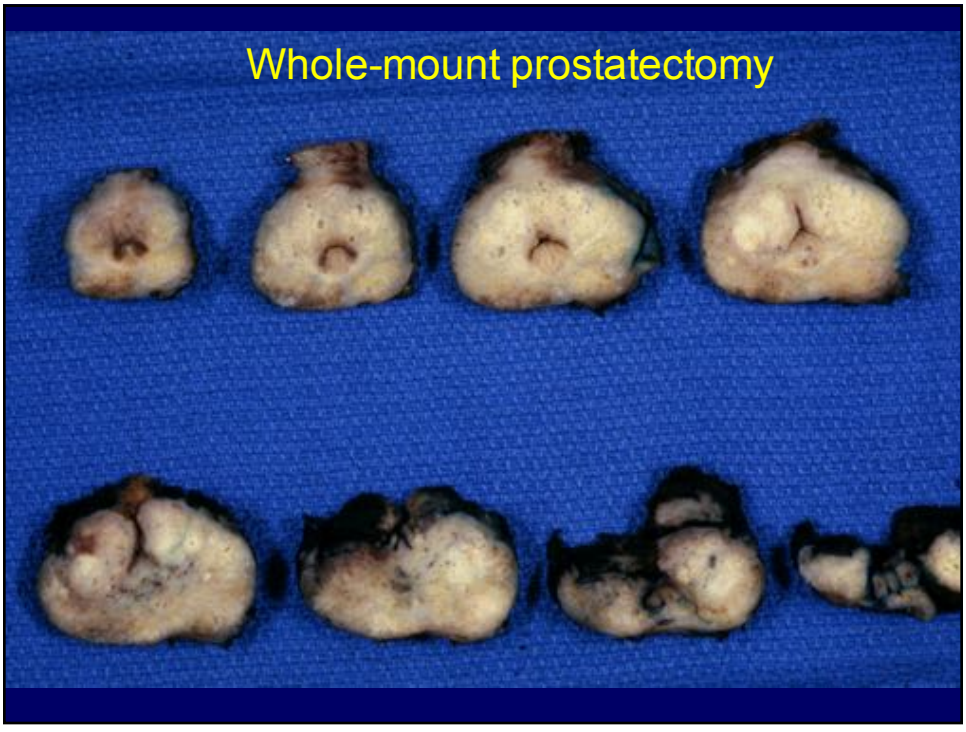


Volume sampled in 12 core biopsy ≈ 0.48%

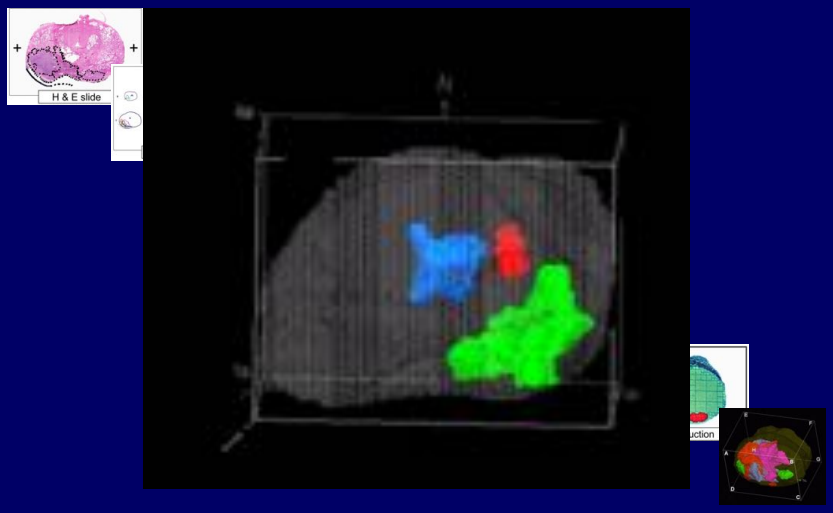
Cancer Sampling on Biopsy: Implications for Choice of Therapy

- Prostate cancer is a multifocal disease
  - Tumors can arise as high grade or transition from low grade
  - Tumors may not develop concurrently
- Cancer sampling is a function of tumor volume: prostate volume
  - Similarly, sampling of high-grade tumor is a function of high-grade component: prostate volume
- Biopsy may not sample highest grade
- Biopsy is poor staging tool

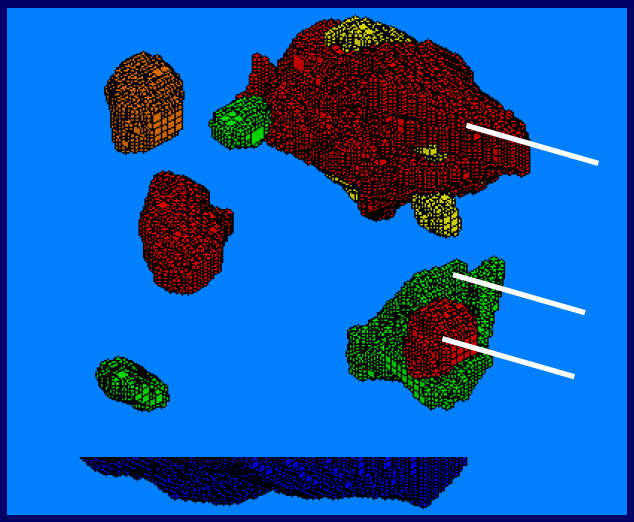
Whole-mount prostatectomy



3-Dimensional Reconstruction of Whole-Mounted Prostatectomy Specimens



3-Dimensional Reconstruction of Prostatectomy: Tumor Multifocality and Heterogeneity



Risk of Pathologic Upgrading or Locally Advanced Disease in Early Prostate Cancer Patients Based on Biopsy Gleason Score and PSA: A Population-Based Study of Modern Patients[*1]

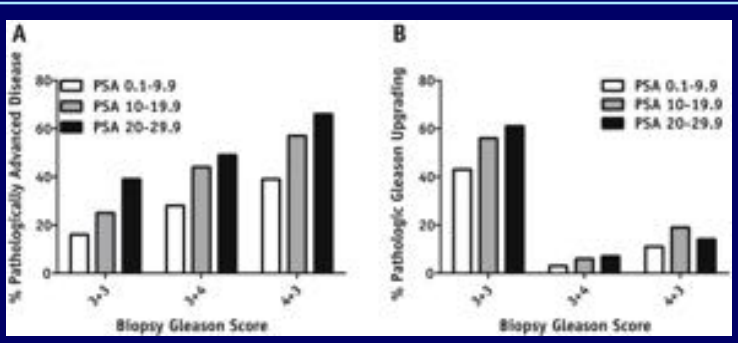


Fig. 1. Percentage of patients who had pathologically advanced disease (A) and Gleason score upgrading (B), stratified by prostate-specific antigen (PSA) concentration and biopsy Gleason score.

*Based on 25,858 patients from the SEER database.

http://dx.doi.org/10.1016/j.ijrobp.2015.01.051
1. Caster JM et al. *Int J Radiation Oncol Phys* 2015;92:244-51

Risk of Progression vs. Overtreatment: What is the Significance of GS6 (ISUP I) Tumor on Biopsy?

Reference	% Upgraded (GS≥7)	% Upstaged (non-OC)	PPV
Griffin et al, 2007	27	16	--
Suardi et al, 2008	37	14	61%
Louie-Johnsun et al, 2009	16	3	39%
Conti et al, 2009	23-35	7-19	--
Mufarrij et al, 2010	46	8	--
Tosoian et al, 2013	13	9	--
Kim et al, 2013	42-51	5-9	45-55%

Identifying Prostate Cancers that can be Treated Conservatively

Concerns

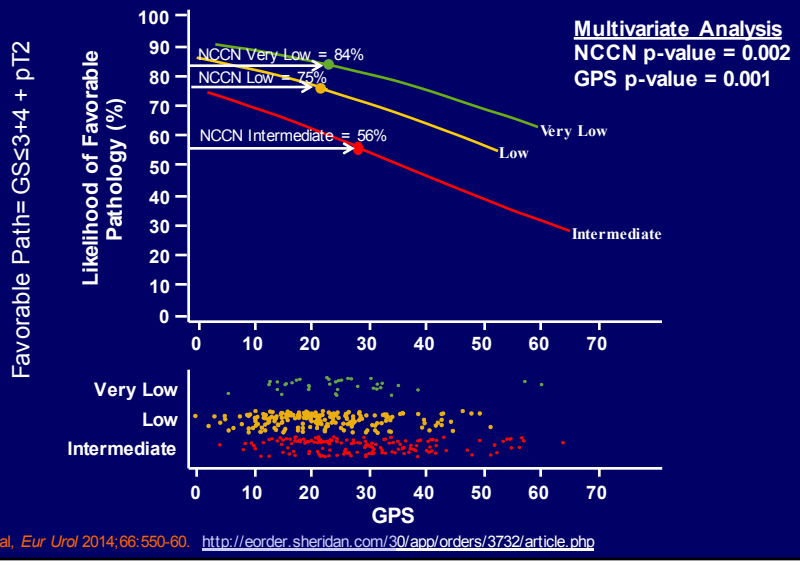
- How can we accurately assess:
  - tumor grade and aggressiveness?
  - tumor extent (multifocality, volume, location)?
- Can we identify "insignificant" cancers?

Potential Solutions on the Horizon

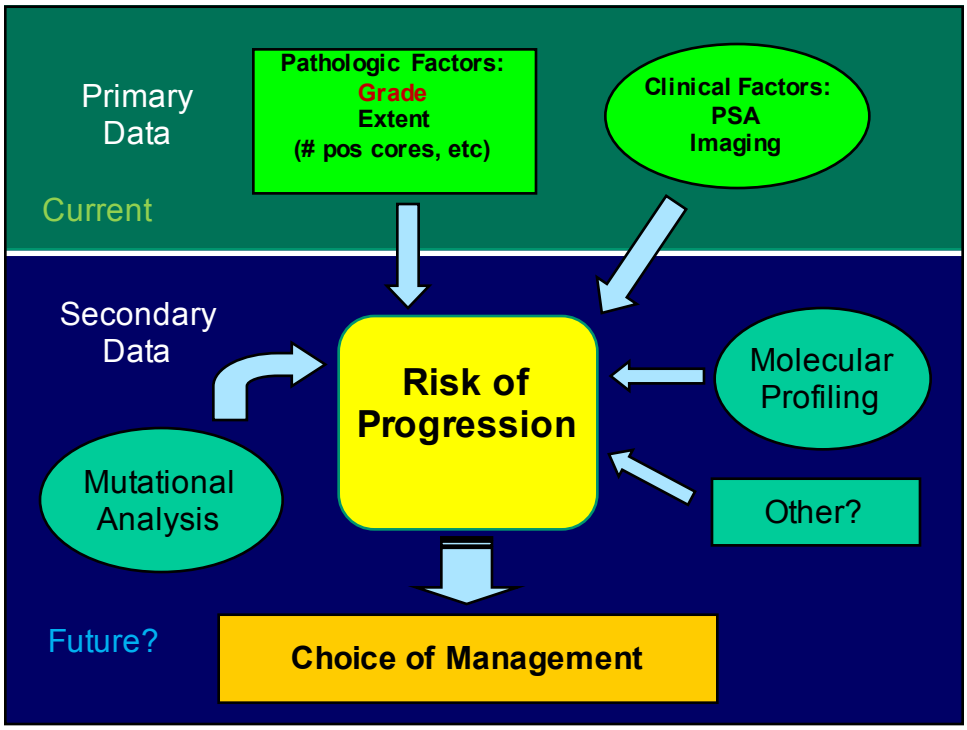
- Improved imaging (mpMRI)
- Thorough sampling: mapping biopsies
- Biomarkers, molecular genetics, gene expression profiling

UCSF Validation Study of GPS

Improved Risk Discrimination with Addition of GPS to NCCN in 395 Men with Very Low-Intermediate Risk Prostate Cancer on Biopsy



Klein EA et al, *Eur Urol* 2014;66:550-60. http://eorder.sheridan.com/30/app/orders/3732/article.php


Primary Data
Pathologic Factors:
Grade
Extent
(# pos cores, etc)
Clinical Factors:
PSA
Imaging
Current
Secondary Data
Risk of Progression
Molecular Profiling
Mutational Analysis
Other?
Future?
Choice of Management