

Prognostic factors of genitourinary tumors: Do we have to care?

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- Introduction
- Prognostic factors
 - Kidney
 - Bladder
 - Prostate
 - Testis
 - Penis
 - ✓ New prognostic/therapeutic markers
- Future Medicine (4 Ps) (5Ps?)

Cancers in Men, 2010, American Cancer Society

Incidence (41%)

■ Prostate	217,730	28%	1 st
■ Urinary Bladder	52,760	7%	4 th
■ Kidney & renal pelvis	35,370	4%	7 th

Estimated deaths (21%)

■ Prostate	32,050	11%	2 nd
■ Urinary Bladder	10,410	3%	9 th
■ Kidney & renal pelvis	8,210	3%	10 th

Prognostic Factors

- ◆ Category I (well supported): stage, grade
- ◆ Category II (extensively studied but not well established): DNA ploidy, nuclear proliferation, angiogenesis, apoptosis, tumor suppressor gene
- ◆ Category III (currently studying): other oncogenes, cytogenetic analysis, growth factors, detection of circulating tumor cells in blood
- ✓ Molecular markers for prognosis, prediction/therapy

Stage (TNM stage)

Primary tumor (T)

- TX Primary tumor cannot be assessed

- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1-T4 Increasing size and/or local extent (depth of invasion) of tumor

Regional lymph nodes (LN)

- NX Regional LNs cannot be assessed
 - N0 No regional LN metastasis
 - N1-N3 Increasing involvement of regional LNs
- * Direct extension into a LN classified as a LN met
- ** Metastasis in other than regional LN as distant metastasis (M)
- *** Tumor nodule: well defined is classified as N; If tumor nodule is ill defined without evidence of residual LN, classified as T extension

Distant metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis
- ✓ MX Distant metastasis cannot be assessed; has been eliminated from AJCC/UICC staging system

Anatomic stage/prognostic groups (stage I-IV): replaced **stage group of 2002 6th AJCC**

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA<10	Gleason≤6
	T2a	N0	M0	PSA<10	Gleason≤6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA<20	Gleason 7
	T1a-c	N0	M0	PSA≥10<20	Gleason≤6
	T2a	N0	M0	PSA<20	Gleason≤7
	T2b	N0	M0	PSA<20	Gleason≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason≥8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

*When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available

Grade (for malignant tumors; Arabic #. 1, 2, 3 not Roman numeral I, II, III)

- Histologic grade (overall proportional)
- ✓ original Broders' grading (4 tier)
- ✓ modified Broders' grading (3 tier)
- ✓ high and low grade (2 tier)
- Nuclear grade (worst areas)
- ✓ Black NG for breast ca.
- ✓ Fuhrman's NG for renal cell ca.
- Combined: FIGO grade for endometrial cancer
- GU tumors: Fuhrman's NG for renal, WHO/ISUP for urothelial ca, Gleason for prostate, no grading for testis, modified Broder's grading for penile cancers

1. Kidney Tumors (RCC)

Five major types

- 1) Conventional (clear cell) RCC
- 2) Papillary RCC
- 3) Chromophobe RCC
- 4) Collecting duct RCC
- 5) Unclassified RCC

Prognostic factors

- Invasion into fat or peri-sinus tissue
- Venous involvement
- Adrenal extension
- Extranodal extension
- Size of metastasis in LN
- Size of largest tumor deposit in LN
- Fuhrman nuclear grade
- Sarcomatoid features
- Histologic tumor necrosis

TNM staging for renal cell carcinoma

T stage

- T1 ≤ 7 cm, limited to kidney
 T1a ≤ 4 cm and T1b $> 4 - \leq 7$ cm
- T2 > 7 cm, limited to kidney
 T2a $> 7 - \leq 10$ and T2b > 10 cm
- T3 invades major veins, perinephric fat, but not beyond Gerota's fascia

- T3a renal vein, perirenal, renal sinus fat
- T3b vena cava below diaphragm
- T3c above diaphragm/invades vena cava wall
- T4 invades beyond Gerota's fascia, **adrenal involvement**

N stage

- N0 no regional LN metastases
- N1 metastases in LN (s): 2002 6th edition N1 and N2 (single vs. multiple)

M stage

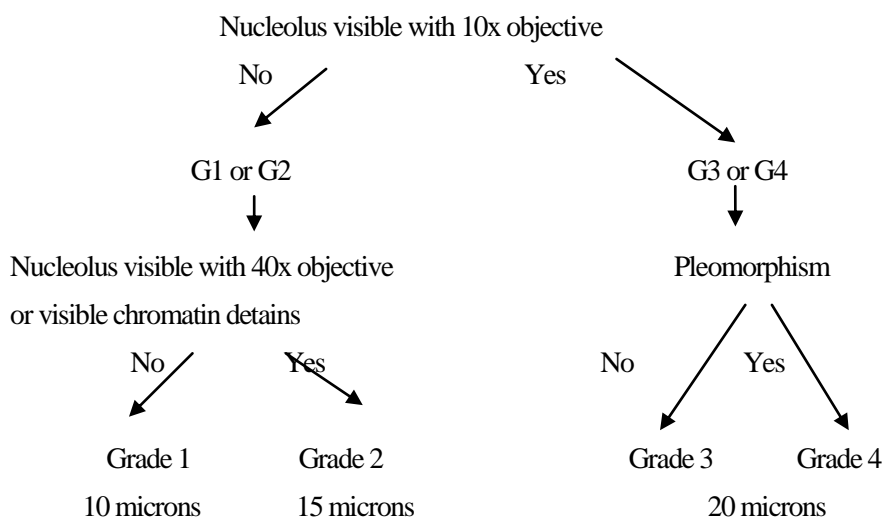
- M0 no distant metastasis
- M1 distant metastasis

Anatomic stage/prognostic groups

- Stage I T1 N0 M0
- Stage II T2 N0 M0
- Stage III T1 or T2 N1 M0
- T3 N0/N1 M0
- Stage IV T4 Any N M0
- Any T Any N M1

Fuhrman nuclear grade

1. Under 10x nucleolus absent NG 1 or 2; present NG 3 or 4
2. Under 40X nucleolus present or chromatin detail NG 2, absent, NG1
3. Nuclear pleomorphism present NG 4, absent NG 3



Chromophobe RCC grading (Based on Geographic nuclear crowding and anaplasia, 3 tier system)

1. Grade 1: chromophobe RCC with (usual) wide constitutive nuclear range but without nuclear crowding and anaplasia (as defined in grades 2 and 3)
2. Grade 2: geographic nuclear crowding (cellular clustering characterized by high geographic nuclear/cytoplasmic density detectable at x10 objective and some nuclei in direct contact with each other when assessed at x40 objective) and the presence of nuclear pleomorphism (size variation of ≥ 3 -fold and distinct nuclear chromatin irregularities, unlike the smudged nuclear atypia of degenerate foci)
3. Grade 3: presence of frank anaplasia (nuclear polylobation, tumor giant cells) or sarcomatoid change.

2. Bladder Cancers

Prognostic factors

- Stage and grade
- Presence or absence of extranodal extension
- Size of the largest tumor deposits in LN
- WHO/ISUP grade
- ❖ WHO/ISUP, high grade/low grade replaced previous 4 tier grading scheme

Summary of changes form 2002 system

- T4 include direct prostatic stromal invasion
- ✓ Subepithelial invasion of prostatic urethra is not T4
- Grading is based on “new WHO/ISUP”
- N stage modified
- ✓ Common iliac node as regional node not “metastatic” lesion

TNM stage for bladder cancer

T stage

- TX tumor cannot be assessed
- T0 no evidence of primary tumor
- Ta papillary non-invasive carcinoma
- Tis carcinoma in situ
- T1 tumor invades subepithelial con. tissue
- T2 tumor invades muscle proper
T2a inner half/T2b outer half
- T3 perivesical fat (T3a, micro; T3b, gross)
- T4 involving prostatic stroma, seminal vesicle, uterus, vagina (4a),
pelvic/abdominal wall (4b)

N and M stage

- N: Lymph nodes
 - Nx lymph nodes cannot be assessed
 - N0 no LN metastasis
 - N1 single LN metastasis in true pelvic LN
(hypogastric, obturator, external iliac, presacral)
 - N2 multiple LN metastasis in true pelvic LN
 - N3 common iliac LN (considered as distant met)
- M: distant metastasis
 - M0 no distant metastasis
 - M1 distant metastasis

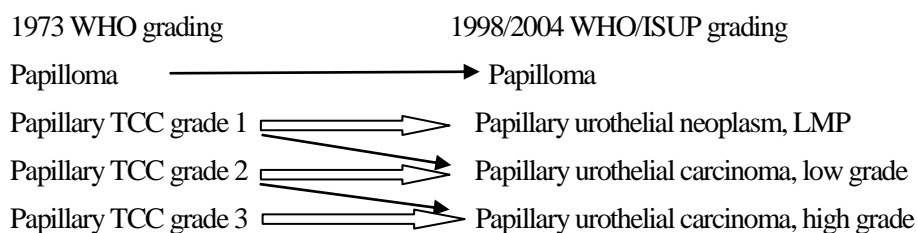
Anatomic Stage/Prognostic Groups

■ Stage 0a	Ta	N0	M0
■ Stage 0is	Tis	N0	M0
■ Stage I	T1	N0	M0
■ Stage II	T2a, 2b	N0	M0
■ Stage III	T3a, 3b	N0	M0
	T4a	N0	M0
■ Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

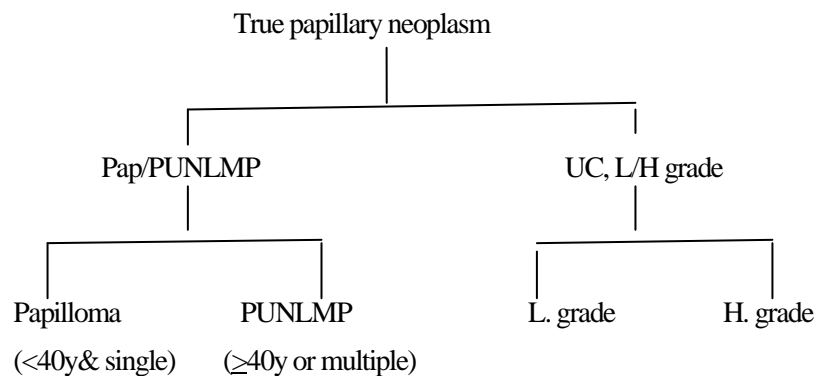
Bladder cancer, general considerations:

- Papillary vs. flat (non-papillary)
 - Grading (WHO/WHO-ISUP)
 - Invasive vs. noninvasive
 - Muscle proper present
 - Lymphovascular invasion
- Muscularis mucosa vs. proper muscle (hyperplastic muscularis mucosae)
- Adipose tissue

WHO/WHO-ISUP grading



Diagnostic Approach of Papillary Tumors (PT)



3. Prostate cancers

Prognostic factors

- Stage and PSA
- Gleason grade
- Gleason primary & secondary patterns
- Gleason tertiary pattern
- Number of biopsy cores examined
- Number of biopsy cores positive for cancer
- Bladder neck invasion: T3a
- Gleason score now recognized as the preferred grading system
- Prognostic factors have been incorporated in Anatomic stage/prognostic groups
- ✓ Gleason score
- ✓ Preoperative PSA

TNM state

T stage

- TX/T0
- T1 clinically inapparent tumor
 - T1a $\leq 5\%$ of tissue resected; T1b $> 5\%$
 - T1c tumor identified by needle biopsy (elevated PSA)
- T2 Tumor confined within prostate
 - T2a involve $\frac{1}{2}$ of one lobe or less
 - T2b more than $\frac{1}{2}$ of one lobe
 - T2c both lobes
- T3 tumor extends through capsule,
 - T3a extracapsular, bladder neck extension (unilateral, bilateral)
 - T3b tumor invades seminal vesicle (s)
- T4 Rectum, ext sphincter, levator muscle, pelvic wall

- ✓ No pathologic T1 classification

N stage

- pNX Regional nodes not sampled
- pN0 No positive regional nodes
- pN1 Metastases in regional node(s)

M stage

- M0 No distant metastasis
- M1 Distant metastasis
- M1a Non-regional lymph node(s)
- M1b Bone(s)
- M1c Other site(s) with or without bone disease

Anatomic stage/prognostic groups (stage I-IV)

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA<10	Gleason≤6
	T2a	N0	M0	PSA<10	Gleason≤6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA<20	Gleason 7
	T1a-c	N0	M0	PSA≥10<20	Gleason≤6
	T2a	N0	M0	PSA<20	Gleason≤7
	T2b	N0	M0	PSA<20	Gleason≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason≥8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

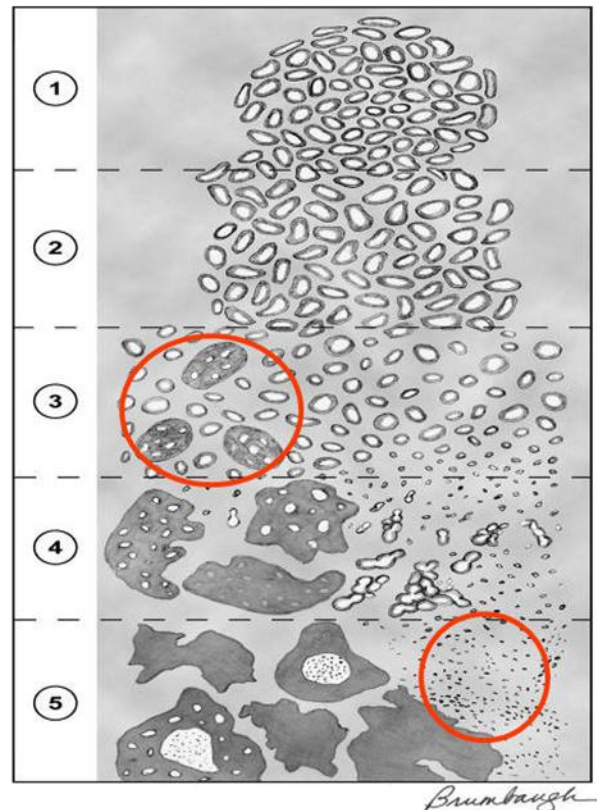
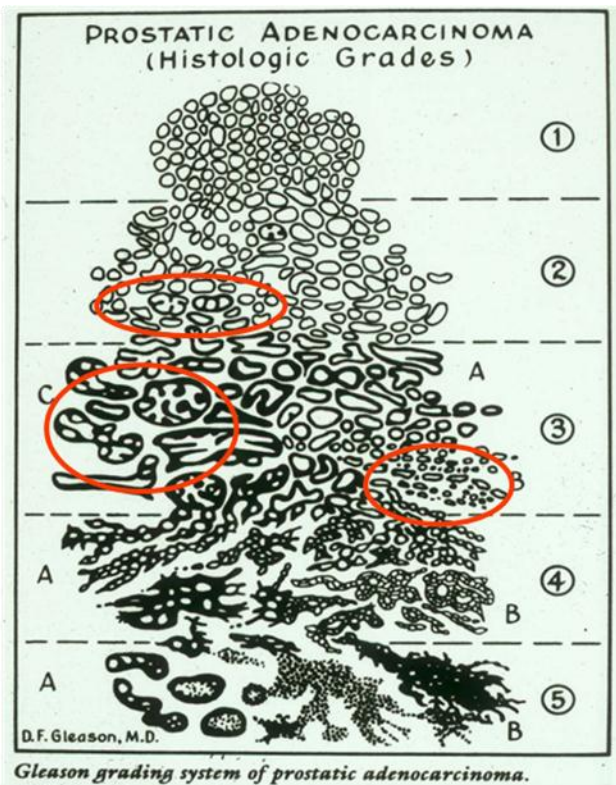
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Gleason grading

Three principles

- 1) Nodular vs. infiltrative: pattern 1, 2 vs. 3-5
- 2) Isolate glands vs. fused glands, incomplete glands
- 3) Cribriform gland with or without necrosis
 - Isolated cells

- *: All cribriform carcinomas are graded at least Gleason pattern 4 (new Gleason grading)



4. Testis tumor

Prognostic factors

- Serum tumor markers
 - ✓ Should be measured prior to orchiectomy
 - ✓ Stage IS—persistent elevation of serum markers following orchiectomy
- Size of largest met in LN
- Radical orchiectomy performed

TNM stage

T stage

- pT0 no evidence of tumor (e.g. scar)
- pTis intratubular germ cell neoplasia
- pT1 limited to testis and epididymis (no vascular invasion).
May invade tunica albuginea but not tunica vaginalis
- pT2 T1 c vascular or t. vaginalis invasion
- pT3 spermatic cord c or s v. invasion
- pT4 scrotum c or s v. invasion

N stage

- N0 no LN metastasis
- N1 ≤ 5 LN metastasis, none ≤ 2 cm
- N2 1 or > 5 LN met, > 2 cm but ≤ 5 cm; +ENE
- N3 > 5 cm metastasis

M stage

- M0 no distant metastasis
- M1 distant metastasis (M1a, nonregional LN or lung; M1b, other sites)

Serum tumor markers

	LDH		hCG mIU/ml		AFP (ng/ml)
■ S1	$<1.5 \times N$		and $<5,000$	and	$<1,000$
■ S2	$1.5-10 \times N$	or	$5,000-50,000$	or	$1,000-10,000$
■ S3	$>10 \times N$	or	$>50,000$	or	$>10,000$

Anatomic stage/prognostic groups

Group	T	N	M	S (Serum Tumor Markers)
Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/Tx	N0	M0	S1-3 (measured post orchiectomy)
Stage II	Any pT/Tx	N1-3	M0	SX
Stage IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
Stage IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
Stage IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
Stage III	Any pT/Tx	Any N	M1	SX
Stage IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
Stage IIIB	Any pT/Tx	N1-3	M0	S2
	Any pT/Tx	Any N	M1a	S2
Stage IIIC	Any pT/Tx	N1-3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

Grading: No grade for testicular tumors

Seminoma	NSGCT
■ 46-53% of GCT	47-54% of GCT
■ bilaterality (2%)	< 2%
■ 35-45 years of age	10 years younger
■ hemorrhage & necrosis—infrequent	frequent
■ cord invasion (5-8%)	20%
■ uniform growth	various patterns
■ distinct cell border	indistinct/overlapping
■ FV septa, lymphocyte, granuloma +++	rare
■ CK - or focal +	CK diffuse +

Important prognostic factors

- Seminoma
- ✓ Tumor size
- ✓ Rete testis invasion
- Non-seminomatous germ cell tumor
- ✓ % of embryonal carcinoma
- ✓ Vascular invasion

5. Penile cancers

Prognostic factors

- Involvement of corpus spongiosum
- Involvement of corpus cavernosum
- % of tumor that is poorly diff.
- Verrucous carcinoma, depth of invasion
- Size of largest LN metastasis
- Extranodal/extracapsular extension
- HPV status

TNM Stage

T stage

- TX primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- Ta non-invasive verrucous carcinoma
- T1 tumor invades subepithelial con tissue:
1a, without LVI and not PD cancer (G1-2); 1b, with LVI or PD cancer (G3-4)

- T2 tumor invades corpus spongiosum or corpora cavernosa
- T3 tumor invades urethra*
- T4 tumor invades other adjacent structures: * Prostatic invasion now T4

N stage

- pNX regional LN cannot be assessed
- pN0 no regional LN metastasis
- pN1 metastasis in single inguinal LN
- pN2 metastasis in multiple or bilateral inguinal LN
- pN3 extranodal extension of LN met or pelvic LN, unilateral or bilateral
- ✓ Clinical N stage based on palpation, imaging
- ✓ No superficial and deep inguinal distinction

M stage

- M0 No distant metastasis
- M1 distant metastasis

* LN outside true pelvis: M

Anatomic stage/prognostic groups

■ Stage 0	Tis, Ta	N0	M0	
■ Stage I	T1a	N0	M0	
■ Stage II	T1b, 2, 3	N0	M0	
■ Stage IIIa	T1-3	N1	M0	
	IIIb	T1-3	N2	M0
■ Stage IV	T4	Any N	M0	
	Any T	N3	M0	
	Any T	Any N	M1	

Grading of penile carcinomas

- Broders' 4-tier system
- Modified Broders' grading, 3 tier system

Future medicine (4Ps)

1. Prevention (precursor conditions)]
2. Prediction (prognostic/predictive markers)
3. Personalized medicine
4. Participatory medicine
5. (?) Pathology in center

Personalized targeted therapy

- Right patient
- Right drug
- Right time
- Right doctor (pathologist)

Essential to perform multidisciplinary team approach

- Recognition of patients' needs
- Clarifying the responsibility
- Respect for each other
- Revision whenever necessary
- Keeping good communication with “Good Team Work”

Take Home Message (summaries)

- Prognostic factors in GU tumors
- Stage and grade
- New prognostic/therapeutic markers
- Multidisciplinary team approach
- Future medicine (4 Ps) (5Ps?)