Staging and Reporting of Prostate Cancer: Major Changes in 8th Edition AJCC Staging and CAP Cancer Checklists

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Genitourinary Pathology in 2016…

CANCER PROTOCOL TEMPLATES
Important Changes in Prostate Cancer Classification, Grading, Staging and Reporting

• New Entities
  o Intraductal carcinoma of the prostate (IDC-P)

• Grading
  o Gleason grade and prognostic grade grouping are both required

• Staging
  o pT2 no longer substaged into pT2a-c

• Reporting
  o Tertiary pattern
  o % pattern 4
  o Multifocal tumors
Intraductal Carcinoma of the Prostate (IDC-P)

Current Concept

• A distinct entity in 2016 WHO classification
• Atypical secretory cells that grow within and significantly expand prostatic ducts and acini
  o Retrograde spread of PCa cells into prostatic glands in majority of cases
  o Precursor to PCa in rare cases
Intraductal Carcinoma of the Prostate (IDC-P)

Two Histological Hallmarks

1. Expansile growth of atypical cells
   • Cribriform/solid architecture

2. Within native prostate glands
   • Basal cell layer at least partially preserved
Intraductal Carcinoma of the Prostate (IDC-P)
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Intraductal Carcinoma of the Prostate (IDC-P)

Marked variation in nuclear size

Pleomorphic nuclei >6X adjacent nuclei
Diagnostic Criteria for IDC-P
(Guo CC and Epstein JI, Mod Pathol. 2006)

- Large glands with growth of atypical cells that span the entire lumen and preserved basal cells

- Solid architecture
- or
- Dense cribriform
- or
- Non-focal comedonecrosis (>1 gland)
- or
- Marked atypical nuclei >6X adjacent benign nuclei

- YES
- IDC-P
- NO
- Atypical intraductal proliferation
Intraductal Carcinoma of the Prostate (IDC-P)

Clinical Significance

• In radical prostatectomy, IDC-P is usually associated with high grade and volume PCa; indicates a worse prognosis
• IDC-P in needle biopsy is almost always associated with invasive PCa and may predict a worse pathologic findings in RP
• Isolated IDC-P without concomitant invasive cancer on needle biopsy is rare but generally warrants definitive treatment (Guo & Epstein Mod Pathol 2006; Robinson & Epstein J Urol, 2010)
• CAP checklist: do not grade; report when present
Gleason Grading for Prostate Cancer

- Dr. Donald Gleason, 1966
- Grading based on the architectural resemblance to benign glands, low-medium magnification
- 5-tier grades (patterns)

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-formed</td>
<td>Less well-formed</td>
<td>Poorly-formed</td>
<td>No glands</td>
<td></td>
</tr>
</tbody>
</table>

- Remains as the single most important prognostic parameter
- Used in all risk stratification tools for treatment decision
Modification of Gleason Grading for PCa
Modification of Gleason Grading for PCa

2005/2014 ISUP Modification of Gleason Grading System: Key Changes

• Definition
  o Each Gleason pattern was more precisely defined
  o Grading cribriform cancer glands
  o Grading new entities/variants

• Reporting
  o Reporting secondary pattern of lower grade when present to a limited extent
  o Reporting secondary pattern of higher grade when present to a limited extent
  o Tertiary pattern
  o Percent of pattern 4/5
  o Radical prostatectomy with separate tumor nodules
  o Needle biopsy with different cores showing different grades
Impact of Modified Gleason Grading System

• Upward shift in Gleason score and risk stratification
  o Practically eliminated grade 1 and 2; 336 lowest score on biopsy
  o Restricted grade 3 and expanded grade 4 spectra

• Artificial improvement in prognosis due to grade migration (Will Rogers phenomenon)

• Improved inter-observer reproducibility among pathologists (from 60 to 80%)

• Improved biopsy–PR concordance

• Impact on treatment
  o GS7 (with limited pattern 4) may be eligible for active surveillance
  o More high grade PCa patients eligible for RP
Limitations of Gleason Grading System (Both Original and Modified)

• Gleason score does not accurately reflect disease aggressiveness
  o GS 2-5 are virtually non-existant and should not be diagnosed on biopsies
  o GS 6 is the lowest score currently assigned

• Use of inaccurate grade combinations for prognosis and therapy
  o 2-4; 5-7; 8-10 (Prostate Cancer Outcome Study) *(N Engl J Med 2013; 368: 436-445)*
  o 2-6; 7-10 (Prostate Cancer Prevention Trial & Prostate Cancer Intervention vs Observation Trial) *(N Engl J Med 2014; 370: 932-942)*
  o 2-6; 7; 8-10 (Scandinavian Prostate Cancer Group Study) (NCCN) (D’amico classification system)
A New Grading System for Prostate Cancer: Grade Grouping

• Proposed by J Epstein (Johns Hopkins)

• Grade grouping **not a new grading method**; based on Gleason system; a novel way to group Gleason grades
  
  o Grade group 1 (GS≤6)
  o Grade group 2 (GS=3+4)
  o Grade group 3 (GS=4+3)
  o Grade group 4 (GS=8)
  o Grade group 5 (GS=9-10)

• Also referred to as International Society of Urological Pathology (ISUP grade) in some publications
# Prognostic Grade Group System (ISUP & WHO)

| Grade group 1 | GS ≤6 | Only individual discrete well-formed glands |
| Grade group 2 | GS 3+4=7 | Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands |
| Grade group 3 | GS 4+3=7 | Predominantly poorly-formed/fused/cribriform glands with a lesser component of well-formed glands |
| Grade group 4 | GS 4+4=8 | Only poorly-formed/fused/cribriform glands |
| | GS 3+5=8 | Predominantly well-formed glands with a lesser component lacking glands |
| | GS 5+3=8 | Predominantly lacking glands or with a lesser component of well-formed glands |
| Grade group 5 | GS 9/10 | Lacks gland formation (or with necrosis) with or w/o poorly-formed/fused/cribriform glands |

Epstein JI et al. AJSP 2016;40: 244-252
Data from 5 centers
19865 RPs since 2005
Epstein et al, Eur Urol, 2015
New Grading System for Prostate Cancer: Grade Grouping

In Radical Prostatectomy…

• Grade group 1 (GS 336) = Excellent prognosis with no risk of metastasis
• Grade group 2 (GS 347) = Very good prognosis, rare metastasis
• Grade group 3 (GS 437) = significantly worse prognosis than grade group 2
• Grade group 4 (GS 8) = bad prognosis, significantly better than group 5
• Grade group 5 (GS 9-10) = worst prognosis
New Grading System for Prostate Cancer: Grade Grouping

- Advantages
  - More accurate stratification than the current system
  - Lower number of categories (5 vs 10 with Gleason)
  - Lowest grade is 1 and not 6

- Accepted by WHO 2016/AJCC
  - Also called ISUP grade in some publications

- Used in conjunction with the Gleason system
  - Prostate adenocarcinoma, Gleason score 3+4=7 (Grade group 2)
Staging of Radical Prostatectomy
Staging of Radical Prostatectomy: T2 Substaging

AJCC, 7th

T2a

T2b

T2c

AJCC, 8th

T2

Clinical stage T2 is substaged as T2a-c based on DRE only.
Pathologic stage T2 is no longer substaged for lack of prognostic significance.
Extraprostatic Extension (T3a)

• Prostate has no true capsule
  o “Capsule” is condensed fibromuscular layer of prostate stroma
  o Best recognized in posterior and posterolateral aspects
    ✓ EPE is defined as presence of PCa beyond confines of prostate gland or PCa glands admixed with periprostatic adipose tissue
  o At apex, anterior and base, “capsule” not readily recognized and contour is irregular
    ✓ EPE is defined as PCa glands at the level of or beyond fat

• When EPE is identified, location and extent should be documented
  o Focal (< one 40x field AND < 2 sections); nonfocal
EPE - Tumor admixed with periprostatic adipose tissue
EPE - Tumor at level of or beyond periprostatic adipose tissue
EPE - Tumor bulging beyond the normal prostate contour
EPE - Tumor at the level or beyond fat (apex, anterior, base)
**Bladder Neck Involvement**

*Microscopic bladder neck involvement* (Zhou M et al, Mod Pathol, 2009)

- Presence of cancer glands within smooth muscle bundles of coned bladder neck without benign prostate glands
- Staged as pT3a, not pT4

**Gross bladder neck involvement**

- T4
Positive Surgical Margins

- Cancer glands touch the ink
- Important to document location and extent of positive margins (linear length)
  - Limited (<3 mm)
  - Non-limited (≥3 mm)
- Optional to report whether positive surgical margin at the site of EPE
- Optional to report the Gleason pattern at the site of positive surgical margin
Reporting of Prostate Cancer
Reporting of Cancer-bearing Prostate Biopsy

• Histologic type (acinar vs. nonacinar and other tumor types)
  o Ductal adenocarcinoma
  o Small cell carcinoma
  o Sarcomatoid carcinoma

• Gleason grade, Gleason score and grade group

• Location of positive cores (biopsy site)

• Tumor quantification

• Other (report only if present)
  o Perineural invasion (PNI)
  o Extraprostatic extension (EPE)
  o Seminal vesicle invasion (SVI)
  o IDC

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Tumor Quantification in Prostate Biopsy

• Number of positive biopsy cores/total number of cores

AND

• % of prostate tissue involved by PCa, or
• Total linear length of cancer/Total length of all biopsy cores

• Any method works equally well if consistently applied
• CAP does not endorse any particular method
Measuring Discontinuous Foci of PCa in Biopsy Core

- Discontinuous involvement by multiple foci of PCa separated by benign tissue is not infrequent in PBx
- No consensus re: the optimal method
  - Adding each foci and ignoring the benign intervening prostatic tissue
  - Assessing discontinuous foci as a single focus
- All methods used in PBx showed excellent correlation with % of tumor at RP
- Linear quantification improved prediction of PCa extent in RP

Schultz et al. AJSP 2013
Reporting Secondary and Tertiary Gleason Patterns

• PCa often has >2 patterns

Rules for reporting secondary and tertiary patterns
• Different for biopsy/radical prostatectomy, and whether the lesser pattern(s) is higher/lower than the more predominant pattern(s)
• Basic rules:
  ✓ 1° should always be included as 1° pattern in GS
  ✓ Higher grade pattern should always be included in GS, either as 2° or 3° pattern, regardless of their amount
Reporting Secondary Gleason Pattern of Lower Grade

- Ignore the lower grade 2\(^o\) pattern when it is <5%
  
  4 96%  3 4%  GS4+4=8

- Include the lower grade 2\(^o\) pattern when it is ≥5%
  
  4 90%  3 10%  GS4+3=7
### Reporting Secondary Gleason Pattern of Higher Grade

**Biopsy**

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
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<tbody>
<tr>
<td>≥5%</td>
<td>Include as 2(^{\circ}) pattern in final GS</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>Include as 2(^{\circ}) pattern in final GS</td>
</tr>
</tbody>
</table>

**Radical Prostatectomy**

1. Include as 2\(^{\circ}\) pattern in final GS, report % (GS 3+4=7 [GP4-2%])
2. Include as 3\(^{\circ}\) pattern in final GS, report %* (GS3+3=6 with 3\(^{\circ}\) pattern 4 [GP4-2%])

* No official recommendation from WHO/ISUP

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Reporting Tertiary Pattern in Biopsy

• When the $3^\circ$ pattern is higher than the $1^\circ$ and $2^\circ$ patterns, it should be included in the final GS as the $2^\circ$ pattern, regardless of its amount

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>3</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td>30%</td>
</tr>
<tr>
<td>5</td>
<td>2%</td>
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</table>

GS $3+5=8$

• When the $3^\circ$ pattern is lower than the $1^\circ$ and $2^\circ$ patterns, ignore the $3^\circ$ pattern

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Percentage</th>
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<tr>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>20%</td>
</tr>
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GS $4+5=9$
Reporting Tertiary Pattern in Radical Prostatectomy

• When the 3° pattern is lower than the 1° and 2° patterns, it should be ignored

• When the 3° pattern is higher than the 1° or 2° patterns
  o If 3° pattern < 5%, include it as 3°, report its %
  o If 3° pattern ≥ 5%, no WHO/ISUP consensus
    1. Include as 2° pattern in final GS, report %*
       (GS 3+5=8 [GP5-10%])
    2. Include as 3° pattern in final GS, report %*
       (GS 3+4=7, with 3° 5 [GP5-10%])
Reporting Percentage of Pattern 4

**Rationale**

- % pattern 4 impacts prognosis
  - 347 vs 437: prognostically distinct
  - Incorporation of % pattern 4 into GS improves risk stratification
- **347 PCa with small volume pattern 4**
  - RP from patients with <5% pattern 4 in 347 PCa diagnosed on biopsy had pathological findings similar to those with 336 PCa in biopsy (Deng et al, AJSP 2015)
  - GS336 and GS 347 PCa with <6% pattern 4 had similar BCR, but < 347 with ≥6% of pattern 4 in PBx (Kir et al. Ann Diagn Pathol 2016)
  - 347 PCa with limited pattern 4 (<5-10%) on biopsy may still be eligible for active surveillance
Reporting Percent Pattern 4

Recommendations

• CAP cancer checklist requires the reporting of % pattern 4 in GS 3+4=7 cancer; optional to report % 4/5 in GS >4+3=7

• No consensus how to record % pattern 4
  o May be reported in 10% intervals, or <5%, 5-10%, 10-25%, 25-50%, 50-75%, >75%
Multifocal Cancer with Different GS Is Common
Multifocal Cancer with Different GS

How do you report:

• Biopsy with multiple cores positive for cancer of different GS?

• Radical prostatectomy with multiple tumor nodules of different GS?
Prostate Biopsy with Multiple Cores of Different GS

- **Core level reporting (ISUP 2005, WHO 2016)**
  - Assign individual GS to separate cores as long as cores are submitted in separate containers, or when they are submitted in the same container but specified for their location by urologist (e.g. by different color inks)

- **Specimen level reporting (CAP)**
  - Assign a GS to all positive cores submitted in the same specimen container

- **Case level reporting (CAP optional)**
  - Global/composite GS optional, method?
Radical Prostatectomy with Multiple Tumor Nodules Showing Different GS

Dominant nodule is reported. Not necessary to report small, organ-confined GS 3+3 foci

- 4+4=8
- NOT GS 4+3=7

Multiple nodule with non-concurrent path parameters- Each major tumor nodule should be graded separately

- 3+3=6
- Two foci of cancer, 4+4=8 and 3+3=6
- NOT GS 3+4=7!
All GU CAP Cancer Protocols Have Been Updated to Include Major Changes in WHO GU Book and 8th Edition AJCC Staging

Prostate Cancer

• New Entities
  o Intraductal carcinoma of the prostate (IDC-P)

• Grading
  o Gleason grade and prognostic grade grouping are both required

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• Reporting
  o Tertiary pattern
  o % pattern 4
  o Multifocal tumors
Thank you!

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