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...

Significant Changes in Prostate Cancer Classification, Grading, Staging and Reporting

- New Entities
  - Intraductal carcinoma of the prostate (IDC-P)
- Grading
  - Grade groups
    - Gleason grade and grade groups are both required
- Staging
  - pT2 no longer substaged into pT2a-c
- Reporting
  - Tertiary pattern
  - % pattern 4
  - Multifocal tumors

Intraductal Carcinoma of the Prostate (IDC-P)

Current Concept

- A new entity in 2016 WHO classification
- Atypical secretory cells that grow within and significantly expand prostatic ducts and acini
  - Retrograde spread of PCa cells into prostatic glands in majority of cases
  - Precursor to PCa in some cases

Intraductal Carcinoma of the Prostate (IDC-P)

Two Histological Hallmarks

- Expansile growth of atypical secretory cells
  - Large, cribriform/solid architecture
- Within native prostate glands
  - Basal cell layer at least partially preserved
Intraductal Carcinoma of the Prostate (IDC-P)

Diagnostic Criteria for IDC-P

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

Marked variation in nuclear size
Pleomorphic nuclei >6X adjacent nuclei

Large glands with growth of atypical cells that span the entire lumen and have preserved basal cells
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 in needle biopsy is rare but generally warrants definitive treatment (Guo & Epstein Mod Pathol 2006; Robinson & Epstein J Urol, 2010)
- CAP checklist: report when present; do not grade IDC

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)

- CAP checklist: report when present; do not grade IDC

Gleason Grading for PCa

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

- Reporting secondary pattern of higher grade when present to a limited extent
- Reporting secondary pattern of lower grade when present to a limited extent
- Tertiary pattern
- Percent of pattern 4/5
- Radical prostatectomy with separate tumor nodules
- Needle biopsy with different cores showing different grades

Modification of Gleason Grading for PCa

- ISUP (2005)/WHO (2016)
- 2005/2014 ISUP Modification of Gleason Grading System: Key Changes

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

- Reporting
  - Reporting secondary pattern of lower grade when present to a limited extent
  - Reporting secondary pattern of higher grade when present to a limited extent
  - Tertiary pattern
  - Percent of pattern 4/5
  - Radical prostatectomy with separate tumor nodules
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Impact of Modified Gleason Grading System

- Upward shift in Gleason score and risk stratification
  - Practically eliminated grade 1 and 2; 336 lowest score on biopsy
  - Restricted grade 3 and expanded grade 4 spectra
- Artificial improvement in prognosis due to grade migration (Will Rogers phenomenon)
- Impact on treatment
  - GS7 (with limited pattern 4) may be eligible for active surveillance
  - More patients with high grade PCa eligible for RP
- Improved inter-observer reproducibility among pathologists (from 60 to 80%)
- Improved biopsy-PR concordance

Limitations of Gleason Grading System

- Gleason score does not accurately reflect disease aggressiveness
  - GS 2-5 are virtually non-existent and should not be diagnosed on biopsies
  - GS 6 is the lowest score currently assigned
- Use of inaccurate grade combinations for prognosis and therapy
  - 2-4; 5-7; 8-10 (Prostate Cancer Outcome Study) (N Engl J Med 2013; 368: 436-445)
  - 2-4; 7; 8-10 (Scandinavian Prostate Cancer Group Study; NCCN; D’amico classification)
A New Grading System for Prostate Cancer: Grade Groups

- Proposed by J Epstein (Johns Hopkins)
- Grade grouping not a new grading method: based on Gleason system; a novel way to group Gleason grades
  - Grade group 1 (GS<6)
  - Grade group 2 (GS=3+4)
  - Grade group 3 (GS=4+3)
  - Grade group 4 (GS=8)
  - Grade group 5 (GS=9-10)
- Also referred to as International Society of Urological Pathology (ISUP grade) in some publications

Grade Grouping for Prostate Cancer (ISUP & WHO)

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

Advantages
- More accurate stratification than the Gleason system
- Lower number of categories (5 vs 10 with Gleason system)
- Lowest grade is 1 and not 6
- Accepted by WHO 2016/AJCC
- Used in conjunction with the Gleason system
  - Prostate adenocarcinoma, Gleason score 3+4=7 (Grade group 2)

Staging of Radical Prostatectomy

Data from 5 centers
19865 RPs since 2005
Epstein et al, Eur Urol, 2015

New Grading System for Prostate Cancer: Grade Grouping

- Advantages
  - More accurate stratification than the Gleason system
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Staging of Radical Prostatectomy (AJCC 8th)

Summary of Changes

<table>
<thead>
<tr>
<th>Change</th>
<th>Outcomes of Change</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of Primary Tumor (T)</td>
<td>Pathologically organ-confined disease is considered T2 and no longer subclassified by extent of involvement or laterality.</td>
<td>III</td>
</tr>
<tr>
<td>Histologic Grade (G)</td>
<td>The Gleason score (2014 criteria) and the Grade Group should both be reported.</td>
<td>II</td>
</tr>
<tr>
<td>AJCC Prognostic Stage Groups</td>
<td>Stage III includes select organ-confined disease tumors based on prostate-specific antigen (PSA) and Gleason/Grade Group status.</td>
<td>II</td>
</tr>
</tbody>
</table>

Staging of Radical Prostatectomy: T2 Substaging

- Clinical T2 substaging as T2a-c based on DRE only; clinically useful
- Pathologic T2 substaging lacks prognostic significance
CAP prostate cancer protocol has also clarified many confusing issues in staging prostate cancer in radical prostatectomy

Extraprostatic Extension (T3a)

- Prostate has no true capsule
  - “Capsule” is a condensed fibromuscular layer of prostate stroma
  - 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
  - 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
  - Focal (< one 40x field AND ≤ 2 sections); nonfocal
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

- Histologic type (acinar vs. nonacinar and other tumor types)
  - Ductal adenocarcinoma
  - Small cell carcinoma
  - Sarcomatoid carcinoma
- Gleason grade, Gleason score and grade group
- Location of positive cores (biopsy site)
- Tumor quantification
- Other (report only if present)
  - Perineural invasion (PNI)
  - Extraprostatic extension (EPE)
  - Seminal vesicle invasion (SVI)
  - IDC

Tumor Quantification in Prostate Biopsy

- Number of positive biopsy cores/total number of cores
- % of prostate tissue involved by PCa
- Total linear length of cancer/Total length of all biopsy cores
- CAP does not endorse any particular method
- Any method works equally well if consistently applied

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
- CAP does not endorse any particular method
- All methods used in PBx showed excellent correlation with % of tumor at RP
- Linear quantification improved prediction of PCa extent in RP

Reporting of Cancer-bearing Prostate Biopsy

- Location of positive cores (biopsy site)
- Tumor quantification
  - % of prostate tissue involved by PCa
  - Total linear length of cancer/Total length of all biopsy cores
- Other (report only if present)
  - Perineural invasion (PNI)
  - Extraprostatic extension (EPE)
  - Seminal vesicle invasion (SVI)
  - IDC
  - IDC

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:
    ✓ 1o should always be included as 1o pattern in GS
    ✓ Higher grade pattern should always be included in GS, either as 2o or 3o pattern, regardless of their amount

Reporting Secondary Gleason Pattern of Lower Grade

- Ignore the lower grade 2o pattern when it is <5%
- Include the lower grade 2o pattern when it is >5%

Reporting Secondary Gleason Pattern of Higher Grade

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Radical Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td>Include as 2o pattern in final GS</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>Include as 2o pattern in final GS</td>
</tr>
</tbody>
</table>

- Include as 2o pattern in final GS, report % (GS 3+4=7 [GP4-2%])
- Include as 3o pattern in final GS, report % (GS3+3=6 with 3o pattern 4 [GP4-2%])

Reporting Tertiary Pattern in Biopsy

- If the 3o pattern is higher than the 1o and 2o patterns, it should be included in the final GS as the 2o pattern, regardless of its amount
- If the 3o pattern is lower than the 1o and 2o patterns, ignore the 3o pattern

Reporting Percentage of Pattern 4

- % 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 2016)
  - GS336 and GS 347 PCa with <6% pattern 4 had similar BCR, but better than 347 with ≥6% of pattern 4 in PBx (Jia et al, Ann Surg 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 cancer
- No consensus how to record % pattern 4
  - May be reported in 10% intervals, or <5%, 5-10%, 10-25%, 25-50%, 50-75%, >75%

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?

Radical Prostatectomy with Multiple Tumor Nodules Showing Different GS

- Dominant nodule is reported
  - Not necessary to report small, organ-confined GS 3+3 foci
  - Multiple nodule with non-concurrent path parameters
  - Each major tumor nodule should be graded separately
  - Two foci of cancer, 4+4=8 and 3+3=6
  - NOT GS 4+3=7!
  - NOT GS 3+4=7!

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 if 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?

All GU CAP Cancer Protocols Have Been Updated to Include Major Changes in WHO GU Book and 8th Edition AJCC Staging

Prostate Cancer

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- Staging
  - pT2 no longer substaged into pT2a-c
- Reporting
  - Tertiary pattern
  - % pattern 4
  - Multifocal tumors

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Prostate Cancer
Thank you!

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