Updates in AJCC/TNM Staging of Prostate Cancer
Samson W. Fine, MD @rovingatuscap
Memorial Sloan Kettering Cancer Center

Disclosure of Relevant Financial Relationships
USCAP requires that all faculty in a position to influence or control the content of CME disclose any relevant financial relationship WITH COMMERCIAL INTERESTS which they or their spouse/partner have, or have had, within the past 12 months, which relates to the content of this educational activity and creates a conflict of interest. Dr. Samson W. Fine declares he has no conflict(s) of interest to disclose.

AJCC 8TH EDITION – PROSTATE TEAM
- Multidisciplinary effort
  - Radiation Oncology
  - Urologic Surgery
  - Urologic Oncology
  - Biostatistics
  - Pathology
- National Cancer Data Base (NCDB)
- Recent publications since 2008 (7th edition)
  - Focus on quality of manuscripts
  - Literature watch from UICC
  - Levels of evidence
  - Guidance: local/national leaders

AJCC Levels of Evidence
- I. Includes consistent results from multiple large, well-designed and well-conducted national/international studies in appropriate patient populations with appropriate end points and treatments. Prospective/retrospective population-based registry studies acceptable.
- II. Is obtained from at least one large, well-designed and well-conducted study in appropriate patient populations with appropriate end points and with external validation
- III. Somewhat problematic because of one or more factors: number, size or quality of individual studies; inconsistency of results across individual studies; appropriateness of patient population or outcomes
- IV. Insufficient because appropriate studies have not yet been performed

How elements were excluded
- Based on available data
  - Critical review of level of evidence
  - Examples of topics that fell below acceptable level:
    - Imaging (e.g. MRI)
    - Molecular markers
  - Imaging (does have a new section):
    - "...inter-observer reproducibility, issues with patient selection and contradictory results have limited the utility of imaging in clinical staging"

Summary of changes: Comparison of 7th & 8th editions
7TH EDITION
- Extraprostatic extension in the form of microscopic bladder neck invasion changed from pT4 to pT3a
- Gleason score (GS) recognized as the preferred grading system
- Prognostic factors incorporated into the AJCC Prognostic Stage Groups (GS, PSA)

8TH EDITION
- Definition of Primary Tumor: pathologically organ-confined disease = pT2, no longer subclassified by extent of involvement or laterality
- Histologic Grade: GS (2014 criteria) and Grade Group [GrdGp] should both be reported
- AJCC Prognostic Stage III includes select OC tumors based on PSA and/or GS/GrdGp
Updates in TNM Staging of Prostate Cancer

Organ-confined disease

- 1992: pT2a, b, c
- 1997: pT2a, b
- 2002: pT2a, b, c
- 2010: pT2a, b, c

Evidence to change pT2 classification

- Substaging does not convey prognostic information
- Poor correlation b/t cT & pT substaging
- Unilateral large tumor would be assigned lower pT stage than 2 small b/l cancers
- Poor reproducibility: <1/2 v. >1/2 lobe

Summary of Changes #1: Definition of Primary Tumor

- Pathologically organ-confined disease is considered pT2 and no longer sub-classified by extent of involvement or laterality (Level of Evidence: III)

Evolution in Prostate Cancer Grading

- ISUP modified 2005
- ISUP 2014

PROGNOSTIC GRADE GROUPS

- 5 institutions
- 21K patients: RP
- 16K patients: NB
- 5.5K patients: RT
- GrdGrp 1 v. GS 6
- discrimination GST
- GrdGrp 2 v. 3

Recurrence-free progression stratified by NB GrdGrp
Recurrence-free progression stratified by RP GrdGrp
Updates in TNM Staging of Prostate Cancer

Summary of Changes #2: Histologic Grade

- Gleason score (2014 criteria) & Grade Group should both be reported (Level of Evidence: II)

<table>
<thead>
<tr>
<th>Grade Group</th>
<th>Gleason Score</th>
<th>Gleason Pattern(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤6</td>
<td>≤3+3</td>
</tr>
<tr>
<td>2</td>
<td>3+4</td>
<td>4+3</td>
</tr>
<tr>
<td>3</td>
<td>4+5 (8)</td>
<td>4+4</td>
</tr>
<tr>
<td>4</td>
<td>9 or 10</td>
<td>4+5, 5+4, or 5+5</td>
</tr>
</tbody>
</table>

The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Definition of Grading Patterns and Proposal for a New Grading System

John A. Eagle Jr., MD, Allen L. Epstein, MD, Philip A. Humphrey, MD, and the ISUP Grading Committee

Revisions to CAP Protocols

- In addition to Gleason patterns and Gleason Score
  - Grade Group
    - Grade group 1
    - Grade group 2
    - Grade group 3
    - Grade group 4
    - Grade group 5

2016 WHO GU Classification

Table 3.03

<table>
<thead>
<tr>
<th>Grade group 1: Gleason score ≤6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only individual discrete well-formed glands</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade group 2: Gleason score 3+4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly well-formed glands with lesser component of poorly formed / fused / cribriform glands</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade group 3: Gleason score 4+3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly poorly formed / fused / cribriform glands with lesser component of well-formed glands</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade group 4: Gleason score 4+4, 3+5, 5+3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly poorly formed / fused / cribriform glands</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade group 5: Gleason scores 6-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack gland formation (or with necrosis) with or without poorly formed / fused / cribriform glands</td>
</tr>
</tbody>
</table>
### AJCC Prognostic Stage Groups

<table>
<thead>
<tr>
<th>Prognostic Stage Group</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>PSA</th>
<th>Grade Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>cT1a-c</td>
<td>pT1a</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>cT2a-c</td>
<td>pT2a</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>IIA</td>
<td>cT1a-c</td>
<td>pT1a</td>
<td>N0</td>
<td>M0</td>
<td>≥ 10</td>
</tr>
<tr>
<td></td>
<td>cT2a-c</td>
<td>pT2a</td>
<td>N0</td>
<td>M0</td>
<td>≥ 10 &lt; 20</td>
</tr>
<tr>
<td>IIB</td>
<td>T1-2</td>
<td>N0</td>
<td>M1</td>
<td>&lt; 20</td>
<td>1</td>
</tr>
<tr>
<td>IIC</td>
<td>T1-2</td>
<td>N0</td>
<td>M1</td>
<td>&lt; 20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N0</td>
<td>M1</td>
<td>≥ 20</td>
<td>2–4</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2</td>
<td>N0</td>
<td>M1</td>
<td>≥ 20</td>
<td>1–4</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N0</td>
<td>M1</td>
<td>≥ 20</td>
<td>1–4</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-4</td>
<td>N0</td>
<td>M1</td>
<td>Any</td>
<td>1–4</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>N0</td>
<td>M1</td>
<td>Any</td>
<td>5</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
<td>N1</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>N1</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

### Summary of Changes #3: AJCC Clinical Prognostic Stage Groups

- **AJCC Stage II further subdivided by Gleason Score/Grade Group**
- **AJCC Stage III includes select organ-confined tumors based on PSA and Gleason Score/Grade Group**

### AJCC-Prostate Registry Data Collection Variables

- Tertiary/Minor Gleason patterns (prostatectomy)
- Number of cores positive / # of cores examined
- For + cores: u/l, b/l, beyond prostate
- Metastatic sites

### Evaluation of Risk Assessment Tools

- 15 available prognostic models evaluated = multivariable model where factors predict a clinical outcome in the future
- 13 models rejected, including all 8 for localized disease
- 2 models met all of the criteria – both based on data from large phase III trials in metastatic pts. that were externally validated

### Precision Medicine Core

**Inclusion/Exclusion Criteria**

- Inclusion Criteria:
  - OS/DSS/DSM
  - Model addresses clinically relevant Q
  - Model includes relevant predictors
  - Validation study: which pts. used to evaluate & data from VDS
  - Generalizability & external validation
  - Well-defined prognostic time zero
  - All predictors known at time zero and clearly defined
  - Sufficient detail to implement model (i.e., equation) or free access to it
  - Measure of discrimination must be reported (usually as CI) on the validation data set (VDS)

- Exclusion Criteria:
  - Insufficient data to implement model
  - Model validated over time frame / in practice setting relevant to contemporary pts.
  - What treatment(s) were applied if any and with what frequency
  - Development / validation of prediction model appears as peer-reviewed journal article

### What's Not Included in AJCC Prognostic Stage Groups

- Tumor Volume
- Extent of extraprostatic extension (EPE)
- Subclassification of (+) Surgical Margins
Tumor Volume/Size

- Well-established correlation with grade, stage, tumor progression
- Visually estimated quantitation and/or maximum diameter
- Fail to show IPV
- No accepted standard for measurement of TV
- Needs to be appropriate for routine clinical practice
- Even "objective" measures subject to issues of:
  - Total v. subtotal embedding
  - Processing effects: shrinkage; irregular sectioning
  - Dominant/index tumor v. overall volume/size

Tumor Quantitation: REC

Tumor Quantitation: REQ

Prostatic Capsule

- Not a true capsule
- Condensation of fibromuscular stroma
- Covers posterolateral prostate
- Anterior / Apex / Bladder neck
- Indistinct
- Not present

PROSTATIC ADENOCARCINOMA

"Prostatic Capsule"

- 10,750 RP pts
- No EPE: 7843 (73%)
- F-EPE: 1258 (12%)
- NF-EPE: 1649 (15%)

Urology 2015;85:161-164

Surgical Margin Positivity

AJCC: assign R1

Positive Surgical Margins: Meta-Analysis

J Urol 2009; 182:1357-1363

Number and extent of M+ correlated with BCR
Did not improve predictive accuracy v. +/- margin alone
Further Subclassification of +SM

- Independent Predictive Value for BCR
  - Location
  - Extent
  - One v. multiple
  - Grade at +SM (GG, GS)

- Single institution
- Limited follow up
- Limited # of events

**Lack of randomized study to see if early adjuvant RT = decreased risk of BCR**

Summary of changes for Prostate Cancer AJCC 8th edition

8TH EDITION

- Pathologically organ-confined disease is one category = pT2
- GS (2014 criteria) & Grade Group [GrdGrp] reported
- AJCC Prognostic Stage III includes select OC tumors based on PSA +/- GS/GrdGrp

Opportunities for Pathology

- Large data sets w/ validation
- PSA-recurrence as an acceptable endpoint
- Excellent and independent statistical support
- Collaborative work

Important Information Regarding CME/SAMs

The Online CME/Evaluations/SAMs claim process will only be available on the USCAP website until September 30, 2017.

No claims can be processed after that date!

After September 30, 2017 you will NOT be able to obtain any CME or SAMs credits for attending this meeting.