Updates in TNM Staging of Prostate Cancer

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Memorial Sloan Kettering Cancer Center
Updates in TNM Staging of Prostate Cancer

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 (and Guiding Principles)
- Guidance of local & national leaders
 Updates in TNM Staging of Prostate Cancer

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 recognized as the preferred grading system
- Prognostic factors incorporated into the 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 [GrdGrp] should both be reported
- AJCC Prognostic Stage Groups: Stage III includes select OC tumors based on PSA and/or GS/GrdGrp
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
- Correlation between cT & pT substaging poor
- Unilateral large tumor would be assigned lower pT stage than 2 small b/l cancers
- Poor reproducibility: <1/2 v. >1/2 lobe

FIGURE 1. Fifteen-year actuarial Kaplan–Meier prostate-specific antigen (PSA) recurrence-free survival curves according to pathologic stage (log-rank test: $P = 0.755$).

**Stephenson et al. Cancer 2004;100:1646-1649**
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 (III)
PROGNOSTIC GRADE GROUPS

**Biopsy Gleason score**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 + 4</td>
<td>2.19 (1.35–3.56)</td>
<td>0.002</td>
</tr>
<tr>
<td>4 + 3</td>
<td>5.38 (3.33–8.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8</td>
<td>6.92 (3.99–11.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9–10</td>
<td>10.27 (5.29–19.92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**RP Gleason score**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6 + Tertiary</td>
<td>1.05 (0.42–2.59)</td>
<td>0.917</td>
</tr>
<tr>
<td>3 + 4</td>
<td>2.81 (1.53–5.18)</td>
<td>0.001</td>
</tr>
<tr>
<td>3 + 4 + Tertiary</td>
<td>2.88 (1.26–6.61)</td>
<td>0.012</td>
</tr>
<tr>
<td>4 + 3</td>
<td>5.66 (3.02–10.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4 + 3 + Tertiary</td>
<td>7.14 (3.75–13.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8</td>
<td>10.31 (5.03–21.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8 + Tertiary</td>
<td>7.70 (3.64–16.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9–10</td>
<td>12.12 (6.40–22.97)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BJU Int 2013; 111:753-760
Updates in TNM Staging of Prostate Cancer

- 5 institutions
- 21K patients: RP
- 16K patients: NB
- 5.5K patients: RT
- GrdGrp 1 v. GS 6
- ↑discrimination
  GS7:
  • GrdGrp 2 v. 3

Multivariable

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref.</td>
<td>2.54</td>
<td>2.18–2.95</td>
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</tr>
<tr>
<td></td>
<td>5.70</td>
<td>4.88–6.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>9.14</td>
<td>7.73–10.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>13.78</td>
<td>11.53–16.47</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Multivariable

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref.</td>
<td>1.94</td>
<td>1.67–2.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>5.14</td>
<td>4.43–5.97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>7.99</td>
<td>6.73–9.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>11.68</td>
<td>9.92–13.76</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Updates in TNM Staging of Prostate Cancer

Br J Cancer 2016;114:1078-1083

Eur Urol 2016;69:1135-1141
Summary of Changes #2: Histologic Grade

- Gleason score (2014 criteria) & Grade Group should both be reported (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>7</td>
<td>3+4</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>4+3</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>4+4 (3+5/5+3)</td>
</tr>
<tr>
<td>5</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

Jonathan I. Epstein, MD,* Lars Egevad, MD, PhD,† Mahul B. Amin, MD,‡ Brett Delahunt, MD,§ John R. Srigley, MD,‖ Peter A. Humphrey, MD, PhD,¶ and the Grading Committee
### Table 3.03

<table>
<thead>
<tr>
<th>Grade group</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Grade group 1:** | Gleason score \( \leq 6 \)  
Only individual discrete well-formed glands |
| **Grade group 2:** | Gleason score \( 3+4=7 \)  
Predominantly well-formed glands with lesser component of poorly formed / fused / cribriform glands |
| **Grade group 3:** | Gleason score \( 4+3=7 \)  
Predominantly poorly formed / fused / cribriform glands with lesser component of well-formed glands |
| **Grade group 4:** | Gleason score \( 4+4=8; \ 3+5=8; \ 5+3=8 \)  
Only poorly formed / fused / cribriform glands  
Predominantly well-formed glands and lesser component lacking glands  
Predominantly lacking glands and lesser component of well-formed glands |
| **Grade group 5:** | Gleason scores 9-10  
Lack gland formation (or with necrosis) with or without poorly formed / fused / cribriform glands |
Updates in TNM Staging of Prostate Cancer

NCCN Guidelines Version 1.2017 Staging Prostate Cancer

GRADE GROUP DEFINITIONS
Grade group 1: Gleason score ≤6
Only individual discrete well-formed glands

Grade group 2: Gleason score 3+4=7
Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands

Grade group 3: Gleason score 4+3=7
Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands

Grade group 4: Gleason score 4+4=8; 3+5=8; 5+3=8
• Only poorly-formed/fused/cribriform glands or
• Predominantly well-formed glands and lesser component lacking glands¹ or
• Predominantly lacking glands and lesser component of well-formed glands¹

Grade group 5: Gleason score 5-10
Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands²

¹Poorly-formed/fused/cribriform glands can be a more minor component
²For cases with >95% poorly-formed/fused/cribriform glands or lack of glands on a core or at RP, the component of <5% well-formed glands is not factored into the grade

References

Note: All recommendations are category IA unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Revisions to CAP Protocols

• In addition to Primary/Secondary/Tertiary Gleason patterns and Total Gleason Score

• Grade Group
  ___ Grade group 1
  ___ Grade group 2
  ___ Grade group 3
  ___ Grade group 4
  ___ Grade group 5
## 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, cT2a</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>pT2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
<td>1</td>
</tr>
<tr>
<td>IIA</td>
<td>cT1a-c, cT2a</td>
<td>N0</td>
<td>M0</td>
<td>≥ 10 &lt; 20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2b-c</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>1</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>2</td>
</tr>
<tr>
<td>IIC</td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>4</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>≥ 20</td>
<td>1–4</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-4</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>1–4</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>5</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>N0</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
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</tbody>
</table>
Do Adenocarcinomas of the Prostate With Gleason Score (GS) \( \leq 6 \) Have the Potential to Metastasize to Lymph Nodes?

Am J Surg Pathol 2012;36:1346-1352

Hillary M. Ross,* Oleksandr N. Kryvenko,† Janet E. Cowan,‡ Jeffry P. Simko,§ Thomas M. Wheeler,|| and Jonathan I. Epstein, MD*†#

Stage I includes a pT staged tumor
### 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, cT2a</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>pT2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 10</td>
<td>1</td>
</tr>
<tr>
<td>IIA</td>
<td>cT1a-c, cT2a</td>
<td>N0</td>
<td>M0</td>
<td>≥ 10 &lt; 20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2b-c</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>1</td>
</tr>
<tr>
<td>IIB</td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>2</td>
</tr>
<tr>
<td>IIC</td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>&lt; 20</td>
<td>4</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>≥ 20</td>
<td>1–4</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-4</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>1–4</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>5</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>N0</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>
Summary of Changes #3: AJCC Prognostic Stage Groups

• Stage II further subdivided by Gleason Score/Grade Group

• Stage III includes select organ-confined tumors based on PSA and Gleason Score/Grade Group (II)
AJCC-Prostate Registry Data Collection Variables

- Tertiary/Limited 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

<table>
<thead>
<tr>
<th>Approved Prognostic Tool</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic castration-resistant prostate cancer treated with</td>
<td>Halabi et al. J Natl Cancer Inst 2013;105:1729-</td>
</tr>
<tr>
<td>second-line therapy</td>
<td>1737</td>
</tr>
</tbody>
</table>
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 sets I/E criteria
- **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 sets (VDS)

**Exclusion Criteria:**
- Substantial proportion of pts. with no follow-up in VDS
- No info on # of pts. w/ missing values in VDS
- # of events in VDS is small
What’s Not Included

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

- Well-established **correlation** with grade, stage, tumor progression
- Visual estimate quantitation and/or maximum diameter
  - Fail to show IPV
- No accepted standard for measurement of tumor volume
  - 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**

<table>
<thead>
<tr>
<th>Intraglandular extent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum size of dominant nodule (mm)</td>
</tr>
</tbody>
</table>

**International Collaboration on Cancer Reporting**

<table>
<thead>
<tr>
<th>Tumor Quantitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of prostate involved by tumor</td>
</tr>
<tr>
<td>Tumor size (dominant nodule, if present):</td>
</tr>
<tr>
<td>Greatest dimension: ____ mm</td>
</tr>
<tr>
<td>+ Additional dimensions: ____ x ____ mm</td>
</tr>
</tbody>
</table>

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Updates in TNM Staging of Prostate Cancer
**PROSTATIC ADENOCARCINOMA**

**Prostatic Capsule**

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

The Prostatic “Capsule”: Does It Exist?
## Prostatic Adenocarcinoma

### Prognostic Factors for PSA Progression

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>P</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop PSA</td>
<td>.001</td>
<td>1.02</td>
</tr>
<tr>
<td>Gleason sum</td>
<td>.001</td>
<td>2.01</td>
</tr>
<tr>
<td>Tumor volume</td>
<td>.704</td>
<td>1.01</td>
</tr>
<tr>
<td>Level of PCI</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Level 3F vs 0-2</td>
<td>.019</td>
<td>2.03</td>
</tr>
<tr>
<td>Level 3E vs 0-2</td>
<td>.001</td>
<td>3.88</td>
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<tr>
<td>SVI</td>
<td>.002</td>
<td>2.00</td>
</tr>
<tr>
<td>+LN</td>
<td>.001</td>
<td>2.55</td>
</tr>
</tbody>
</table>

Wheeler TM et al.  
*Hum Pathol*  
1998; 29:856-862
• 10,750 RP pts.
• No EPE: 7843 (73%)
• F-EPE: 1258 (12%)
• NF-EPE: 1649 (15%)

**Table 2.** Multivariate Cox proportional hazard model of predictors of biochemical recurrence-free survival

| Variables          | HR (95% CI) | P Value
|--------------------|-------------|---------
| Extent of EPE      |             |         
| No EPE             | Reference   |         
| FEPE               | 2.41 (1.87-3.10) | <.0001  
| NF-EPE             | 3.57 (2.89-4.40) | <.0001  
| Margin status      | Reference   |         
| Negative           | Reference   | .792    
| Positive           | 0.99 (0.99-1.00) | .479    
| Lymph node status  | Reference   |         
| Negative           | Reference   | .992    
| Positive           | 0.99 (0.99-1.00) | .992    
| SV invasion        | Reference   |         
| Negative           | Reference   | 1.00 (1.00-1.01) | .002    
| Positive           | 1.00 (1.00-1.01) | .002    
| Gleason score ≤6   | Reference   |         
| 3 + 4              | 2.83 (2.06-3.89) | <.0001  
| 4 + 3              | 7.33 (5.34-10.07) | <.0001  
| 8                  | 13.4 (9.51-18.8) | <.0001  
| 9-10               | 16.3 (11.7-22.9) | <.0001  
| Gleason score 7+    | Reference   |         

**Table 3.** Cox proportional hazard models for extent of extraprostatic extension stratified by Gleason score in patients with negative margins, no seminal vesicle invasion, and no lymph node metastases

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No EPE</td>
<td>4533</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>FEPE</td>
<td>241</td>
<td>1.78 (0.54-5.84)</td>
<td>.34</td>
</tr>
<tr>
<td>NF-EPE</td>
<td>88</td>
<td>4.88 (1.48-16.03)</td>
<td>.009</td>
</tr>
<tr>
<td>Gleason score ≤6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No EPE</td>
<td>1871</td>
<td>Reference</td>
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<tr>
<td>FEPE</td>
<td>343</td>
<td>1.15 (0.56-2.40)</td>
<td>.694</td>
</tr>
<tr>
<td>NF-EPE</td>
<td>290</td>
<td>2.82 (1.58-5.03)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gleason score 7+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No EPE</td>
<td>557</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>FEPE</td>
<td>158</td>
<td>1.33 (0.71-2.51)</td>
<td>.374</td>
</tr>
<tr>
<td>NF-EPE</td>
<td>187</td>
<td>1.74 (1.04-2.94)</td>
<td>.035</td>
</tr>
</tbody>
</table>
Surgical Margin Positivity

Tumor at inked margin in an area of capsular incision

Tumor at inked margin in an area of extraprostatic extension

pT2, +SM

pT3a, +SM
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
    - Length in mm
  - Grade at +SM (GG, GS)
- Limited follow up
- Limited # of events

**Lack of randomized study to see if early adjuvant RT = decreased risk of BCR**
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.
Updates in TNM Staging of Prostate Cancer: References


NCCN Guidelines Version 1.2017 Staging – Prostate Cancer


