Pathological Information Needed From RP Specimen For Locally Advanced Disease: Margins, Lymph Nodes, and What Else?

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Disclosures

• Research/Consulting: AbbVie, Amgen, Astellas, Bayer, Dendreon, Ferring, Genomic Health, Innocrin, Inovio, Janssen, MDxHealth, Myovant, Myriad, Neogenomics, Pfizer, Sanofi, Tolmar

• Stocks/Equity: None
RP Goals:

- Low Risk: PSA <10, Gleason ≤ 6, and clinical stage T1 or T2
- Intermediate Risk: PSA 10-20, and/or Gleason 7
- High Risk: PSA > 20, Gleason ≥ 8, or clinical stage ≥T3

- (a) eradication of the cancer with negative surgical margins, (b) preservation of urinary function, and (c) preservation of erectile function, when appropriate.

- Positive surgical margins may be associated with higher rates of cancer recurrence; surgical techniques (preservation of urinary and erectile function) may result in positive margins

- How can the pathologist optimize assistance? Implications for adjuvant (precision/personalized) therapy? Clinical trial enrollment?
Surgeon Needs

- Trifecta: Cured, Potent, & Continent Patient
- Pathologic Information: Likelihood Adjuvant Therapy; Additional Molecular tests?
- Musts vs Maybes
- No intraoperative or postoperative complications
- No calls after dinner hours
- Endless adulation
Pathologic Features of High Risk for Prostate Cancer Progression Following Prostatectomy

- Gleason grade 8-10
- Stage $\geq$ pT3a
- Margin positive
- LN positive
Significance of Tertiary (<5%) HG Gleason Pattern*

The impact of TP5 of Gleason score 7 in radical prostatectomy specimens is still significant using contemporary grading. Moreover, TP5 was independently associated with biochemical recurrence. However, 3+4=7 with TP5 behaves like 4+3=7 in terms of biochemical recurrence-free survival rate.

Borhan, Epstein. Significance of Gleason Score 7 With Tertiary Pattern 5 at Radical Prostatectomy Urology 2017; 100: 175-9

HG = high-grade
The overall Gleason score is based on the core with the highest Gleason score. Gleason scores can be grouped and range from Prognostic Grade Group I (most favorable) to Prognostic Grade Group V (least favorable).

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Prognostic Grade Group</th>
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<tbody>
<tr>
<td>≤ 6</td>
<td>I</td>
</tr>
<tr>
<td>3 + 4 = 7</td>
<td>II</td>
</tr>
<tr>
<td>4 + 3 = 7</td>
<td>III</td>
</tr>
<tr>
<td>8</td>
<td>IV</td>
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<tr>
<td>9-10</td>
<td>V</td>
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</table>

• 2014 ISUP (Nov. 2014, Chicago)
  – Voted to adopt 5-tiered system (90% consensus)
  – Recommended that percent high grade patterns be specified for groups II and III
  – All modifications to Gleason system should be used in classification
Predicting 15-year prostate cancer specific mortality after radical prostatectomy

- Margin status not independently associated with PCSM

N=23,910 across 5 institutions

Surgical Margins

- Positive margin one vs multiple sites
- Report location (improve technique), albeit no incontrovertible evidence specific site predicts dz progression
- Extent tumor @PSM (3mm cutpoint or negative – focal-extensive) correlates: recurrence rate 14 vs 53% (Emerson); 87-60-35, 5 yr recurrence free (Epstein)
- Consensus: report extraprostatic extension (mm) but no need report Gleason score

International Society of Urological Pathology, '05, '09, ‘14
High percent tumor volume predicts biochemical recurrence after radical prostatectomy in pathological stage T3a prostate cancer with a negative surgical margin\(^1\)

Cribiform cancer highly associated with biochemical recurrence in men treated with prostatectomy

Lymph Nodes

Standard PLND should be mandatory in high-risk patients and is recommended for the intermediate group.

- Standard PLND: include all lymphatic tissue along the external iliac vein from the lymph node of Cloquet distally to the bifurcation of the common iliac vein proximally and includes all lymphatic tissue in the obturator fossa.

- Evidence and opinions on the role of extended PLND in high-risk patients are divided. An ePLND may entail the removal of lymph nodes medial and lateral to the internal iliac vessels up to and around the bifurcation of the common iliac artery, with the genitofemoral nerve as the lateral limit.

International Society of Urological Pathology, '05, '09, '14
ePLND

- Extending landing sites potential disease beyond obturator fossa to hypogastrique to external iliacs to presacral?
- Morbidity vs disease control (Ex. Bladder Ca)
- Inadequate templates, different surgeons and single institution series
- Briganti (EAU’15) 5% In risk nomogram, ePLND as the standard

Seminal Vesicles and Lymph Nodes

- LNs: frozen sections only of value high risk (proceed with RP? Pendulum shift eradicate oligometas?)
- LNs: submission vs optimal sampling varies greatly.
- Diameter largest ln more predictive than # pos lns or extranodal extension.

International Society of Urological Pathology, '05, '09, '14
Specimen Handling

• What is the ideal warm ischemia time (time without fixation), to avoid altering protein, DNA, or RNA confirmation, whilst preserving microscopic/immunohistochemical features?
• Fresh samples—avoid formalin effect quality nucleic acids (fragmentation) and proteins (cross linking), impact future assay analytes
• Implications commercially and research available genomic assays?
• pT0: 0.07-4.2% (neoadjuvant endocrine therapy vs mix up, thus ensure supply chain integrity)
• Cost and Time

International Society of Urological Pathology, '05, '09, '14
Fig. 1. Landscape of somatic copy number alterations from 426 prostate cancer cases ordered by prognostic grading group from 1 (low) to 5 (high). Blue denotes deletions; red denotes amplifications.

Molecular Assays

- Prolaris (CCP Score); Decipher (Gene Classifier)
- Increase DNA RM defects & T3 dz Castro et al., JCO ’13
- Alleles associated progression risk; e.g., HSD3B1 genotype (variant vs wild type): point mutation may influence gonadal vs adrenogenic therapeutic response, inform trial selection vs adjuvant ADT (+/- ARSI)
- Who will order: surgeon or pathologist?

Hearn et al, Lancet Oncol. 2016, 17(10):1435
Conclusions

- Cancer grade is a strong indicator of prognosis
- The 5-tier Prognostic Grade Groupings proposed by the 2014 ISUP offer excellent prognostic stratification
  - Easily understandable
  - Validation studies have confirmed clinical utility
- Patients considered as high risk for progression following prostatectomy represent a heterogeneous group
  - Many will not develop metastasis or die of prostate cancer
  - Molecular assays to inform intensity monitoring, adjuvant therapy, and clinical trials
Conclusions

- High Gleason score, seminal vesicle invasion and LN metastasis are adverse pathological features that portend a higher risk of PCSM
- The impact of positive surgical margins is controversial
  - Location, extent and grade of tumor at margin may improve prognostic value
- Tumor volume, particularly of high grade component, may impact risk of progression
- Emerging role for biomarkers to improve risk stratification
Real World Pathology Concerns

- Cost, time and accessibility: additional sampling and assays
- Enhancing expertise and uniformity of technique/interpretation: community vs GU Pathologist
- Integrative strategies: surgeon and pathologist, transition value based care
- Cancer tissue preservation: “Save The Tumor”
Thank You

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