Atypical Glandular Lesions of the Prostate

Objective

• To identify histological abnormalities in prostate specimens and accurately classify them as benign, suspicious, or malignant

Atypical/Atypia

• Irregular or not conforming to type (Dorland’s Illustrated Medical Dictionary, 31st ed, p 180)

• Has had a variety of uses ranging from completely benign (monstrous nuclei in seminal vesicle) to indicating a significant risk for developing malignancy (breast)
Atypia in Breast specimens

• “Some but not all of the requisite features for ductal carcinoma in situ” DuPont and Page NEJM.1985;312:146-51.
• This lead to the use of atypical hyperplasia in helping to identify patients at high risk for breast cancer (i.e., Hartmann LC et al NEJM. 2005;July 21;353:229-237.

Atypia in Prostate

• AKA ASAP ATYP
• Atypical Small Acinar Proliferation (ASAP)
• Atypical Glands Suspicious for Malignancy (ATYP)

Now being recognized as a diagnosis of “suspicious but not diagnostic for malignancy”. Patients with this diagnosis have a 17-70% (many studies place it 40-45%) chance of being diagnosed with cancer on rebiopsy.

For the rest of this presentation lets call it “ASAP”

ASAP

• “Quantitatively and/or qualitatively insufficient for definitive diagnosis or exclusion of prostatic carcinoma” Paner,Gladell P, Jimenez, Rafael E, and McKinney Jesse p 3-95 in Diagnostic Pathology Genitourinary 2010 Amirsys Publishing Edited by Mahul B. Ahmin.
ASAP

- Seen in 2-5% of prostate needle biopsies.
- Many cases represent undersampled cancer.
- Should prompt re-biopsy if clinically feasible.

ASAP Difficulties in Diagnosis

- Present at the edge of a biopsy.
- Artifactual distortion
- Poor fixation, histology etc.
- Inadequate sections

Intervening (interval) unstained sections

- Sections cut between stained slides on all prostate biopsies.
- If ASAP is seen, interval slides rather than recuts are used for special stains, hopefully giving the pathologist a thorough section examination of the tissue and minimizing the chance a small area of ASAP will be cut through.
- But 95% of the time the interval slides will not be needed.
- Should we use routine interval unstained or new recut slides taken only when needed to workup ASAP?
How much difference does it make?

- Hameed O, Humphrey PA. AJCP 2009 May;131(5):683-687
  682 needle biopsy specimens, 38 of which had both interval unstained and new recuts for IHC. ASAP was cut through in 3 (8%) of the interval slides but 19 (50%) of the new recuts.
  Foci of ASAP less than 1 mm were especially in danger of being cut through by new recuts.
  Additional cost of interval slides was $13.20 per case.

Interval Sections cont’d

- Studied 1105 prostate needle biopsy cases, all of which had interval sections. IHC staining for HMWCK was done on 94 (8.5%).
- In 74/94 cases there was still available material for new recuts. In 31 of these the ASAP was not present on the new recuts; the original HMWCK for interval slides helped establish a benign (23 cases) or malignant (8 cases) diagnosis, making a difference in 31/1105 or 2.8% of cases.
  Estimated cost savings from these 31 patients being spared a repeat biopsy = $68,200.

Benefits of Interval Slides

- Cost: assume $13.20 cost per case of interval slides for 1105 cases = $14,586.
- Less than the estimated $68,200 of patients spared a repeat biopsy.
- Not to mention the anxiety and discomfort of a repeat biopsy.
Interval Sections vrs new recuts; a difference experience

- Studied 105 biopsy site specimens from 96 patients. Used a basal cell cocktail (p63, cytokeratins 5 and 14) as well as Racemase.
  No specimens showed a change in only the interval sections but 23 (22%) showed a change in only the ASAP workup ordered on recuts.
  This study did emphasize thorough sampling, with 24 sections examined, no shaving or trimming.

Interval Sections

- This technique shows promise but only 47% of GU pathologists reported using it.
- Egevad L, Allsbrook WC, and Epstein JI. Human Path 2006.37(3)292-7

Features favoring a malignant diagnosis in the prostate

- Small glands (most commonly) seen in an infiltrative pattern, possibly between definitely benign glands.
- Minimum number of glands? Some say at least 3, but there is no agreement. More on that later.
- Prominent nucleoli
- Amphophilic cytoplasm
- Sharp luminal border
- Crystalloids
- Mitoses-apoptotic bodies
- No basal cells
Features Pathognomonic of Prostate Carcinoma

• Collagenous micronodules.
• Circumferential perineural invasion.
• Glomerulations.

Features favoring a benign diagnosis in the prostate

• Medium size to large branching glands.
• Cytoplasm and nuclei similar to definitely benign glands.
• Pale clear cytoplasm.
• Luminal undulations.
• Corpora amylacea.
• Intact basal cell layer.

References

• Epstein JI and Netto George J. Biopsy Interpretation of the Prostate. 4th Ed. Wolters Kluwer/Lippincott Williams & Wilkins 2008.
• Bostwick DG and Meiers. Neoplasms of the Prostate. In Urologic Surgical Pathology by Bostwick DG asnd Cheng Liang 2nd Ed. Elsevier Inc 2008
• Paner GP, Jimenez Rafael, and Mckenney Jesse K. Diagnostic Pathology Genitourinary 1rst Ed Amirsys 2010
Histologic examples
Benign, suspicious, and malignant

Central area of crowded small glands

Prominent nuclei--adenocarcinoma
Obvious invasive adenocarcinoma

Atrophic appearing area

S14 looks atrophic but check out the center
Central area of atrophy with abnormal glands on either side

Higher power

ASAP stain
Seminal vesicle

Benign

Looks benign at first glance but check out the small gland in the center.
Definitely abnormal

ASAP

Abnormal small gland in the center
Compare the upper and lower halves of the core on the right.
Upper—somewhat squamoid, some anisonucleosis

Upper—radiation change

Lower half—adenocarcinoma
Central zone

More central zone

Basal cell hyperplasia
Adenocarcinoma

Anything near the center?
Look for abnormalities in different areas.

Adenosis/atrophy
Adenocarcinoma with atrophic features

Looks atrophic, but would look carefully at 4-6 o’clock

Adenocarcinoma with atrophic features

Adenocarcinoma with atrophic features

Adenocarcinoma with atrophic features
Mimickers of Prostate Cancer

- Androgen deprivation effect—small nuclei, clear cytoplasm, prominent basal cell layer

May be patchy; there may be a spectrum of changes including unaffected adenocarcinoma.

Mimickers cont’d

- Cowper’s glands
- Verumontanum gland hyperplasia
- Mesonephric hyperplasia
- Ganglia

Helpful immunostains in evaluating ASAP vrs Adenocarcinoma

- High Molecular Weight CytoKeratin (34betaE12,Cytokeratin 903).
- “Old faithful”, around since the 1980s.
- Stains basal cells of the prostate.
- P63, cytokeratin 5/6 are good markers.
- Cocktails such as PIN-4
Alpha-MethylCoenzyme A Racemase

- Also known as P504S, AMACR.
- Lets call it Racemase.
- An enzyme involved in Beta-oxidation of branched chain fatty acids.
- Cytoplasmic positivity in Prostate Cancer
- May also be positive in PIN, ASAP, papillary Renal Cell Carcinoma, and nephrogenic metaplasia
- May be negative in some prostate cancers, especially the atrophic, foamy gland, and pseudohyperplastic variants.
- Positive in cancers other than prostate (colon for example)

New kid on the diagnostic block—ERG!

- TMPRSS2-Erg gene fusion detected in about 50% of prostate cancers.
- Recent development of a novel anti-ERG immunostain correlates well with this fusion.
- Very helpful in confirming prostate cancer if positive.
- Caveats—staining in lymphocytes, endothelial cells, occasional benign prostate glands.

ASAP

- Indicates a 40-50% risk of cancer on re-biopsy.
- No need to stratify ASAP—“favor benign” “strongly suspicious for malignancy” etc.
- A good idea to add “suspicious for malignancy” to each ASAP diagnosis.
- Try to reserve words such as “atypia,” “glandular atypia” etc for suspicious cases.
- If atypia is used to describe a nonsuspicious case (i.e., changes secondary to inflammation) it is good to use terms such as “reactive” and mention that it is not suspicious for malignancy.
ASAP-reproducibility

- Van der Kwast et al. Variability in Diagnostic Opinion Among Pathologists for Single Small Atypical Foci in Prostate Biopsies AJSP 2010 34(2) p 169-177
- Studied diagnoses of small atypical foci in 20 prostate biopsies
- Initial diagnoses—8 Adenocarcinoma, 8 ASAP, 4 benign
- Benign diagnoses included PIN and Atypical Adenomatous Hyperplasia/Adenosis.
- Digital images of H & E slides in all 20 cases and immunostains in 9 cases were circulated to 12 pathologists (5 expert, 7 reference pathologists of the European Randomized Screening study of Prostate Cancer—let’s call them all around pathologists)

ASAP Reproducibility cont’d

Results

- Experts diagnosed adenocarcinoma more often than all arounds
- In 5 cases experts had diagnoses ranging from benign to ASAP to adenocarcinoma
- In 10 cases the all arounds had the same range of diagnoses.
- All 5 experts agreed on 5 of 20 cases (35%)
- Most of the cases with widespread disagreement had 2-5 atypical glands

ASAP reproducibility—study limitations in article

- Atypical area was not marked on the slides
- Did the study pathologists make the same diagnoses that they would have if patient care had been involved?
- Does virtual microscopy diagnosis correlate with having the actual glass slide under a scope?
ASAP Reproducibility—limitations per VOS

- Was the group of nonexperts comparable to pathology practice as a whole—remember they were reference pathologists for a European Prostate cancer study group.
- The pathologists viewing the images had stains on less than half the cases, and could not get recuts, additional stains etc.

Implications for prostate signout

- What is due diligence in getting consults?
- Recommendations for a second pathologists reviewing all new diagnoses of malignancy—Brimo F, Shultz L, Epstein JI. J Urol 2010 Jul;184:126-30
- If there is a really worrisome ASAP how many people should you show it to?
- The more you show it around, and the more people that agree with you the more secure your diagnosis—but what if you have 2 Adenocarcinoma, 1 ASAP?
- Have to use your best judgement.

Adenosis/Atypical Adenomatous Hyperplasia (AAH)

- Crowded benign glands
- Common in transition zone
- Seen in 2-20% of TURPS
- Commonly multifocal
- May be confused with malignancy
- Does not indicate a definite increased risk of cancer
Adenosis

• Brawn PN. Cancer 1982, Feb 15:49(4):826-33
• Gave attention to abnormal small gland proliferations which are not cancer
• Found “adenosis” in 108 of 2842 prostate specimens
• Described it as “dysplastic” but not indicating an increased risk for malignancy

Approach to any study of small gland abnormalities of the prostate

• Check for uniformity of terminology, diagnostic criteria, patient population, applicability to most pathology practices.
• Brawn’s study was liberal in calling adenosis, and ultraconservative in calling carcinoma. But it did bring attention to the problem and gave it a appropriate name.

Interpersonal communication skills

• Now required for residents evaluations
• Need to report prostatic abnormalities in a clinically relevant, reproducible fashion.
• “When I use a word, it means just what I choose it to mean—neither more nor less” Humpty Dumpty, Through the Looking Glass by Lewis Carroll
• Clinicians are from Mars and Pathologists are from Venus. Prowser SM, Costa J, Homer RJ. Arch Pathology and Lab Med 2000 July;124(7):1040-6
Recommendations Summary

- Use atypia/ASAP/ATYP etc to mean suspicious for malignancy, indicating a 40-50% risk of a cancer diagnosis on rebiopsy
- Don’t use dysplasia, CIS etc
- Be very careful of making a diagnosis of adenocarcinoma when less than 5-6 glands are present.
- Make liberal use of consultants, intra and extradepartmental.

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