Disclosures

• I have nothing to disclose.
OBJECTIVES

• Reporting of prostate cancer pathology,

• Grading of prostate cancer…. Gleason scoring.

• Overview of the deficiencies in the old Gleason scoring system.

• The new Grade grouping system, its validity and its impact on the clinical practice.

• The importance of high Grade PIN and ASAP in a pathology report.
INTRODUCTION

• Prostate cancer is the most commonly diagnosed male malignancy.

• According to the SEER (Surveillance, Epidemiology, and End results) program of the National Cancer Institute (NCI), the 2017 data shows an estimated 161,360 new cases in the United States, representing 9.6% of all new cancer cases and 26730 deaths.

• Prostate cancer accounts for about one-fifth (21%) of all new cancer cases in men in Canada. (http://www.cancer.ca/en/cancer-information/cancer)
INTRODUCTION- CONTD.

• The correct diagnosis and grading is crucial for a patient’s prognosis and therapeutic options.

• The Gleason grading is the most commonly used histological grading system

• Continues to be the single most powerful predictor of prostate cancer prognosis and plays a significant role in clinical management.

• Recommended by the World Health Organization.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Clinically inapparent; tumor not palpable or visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>Incidental finding during transurethral resection of prostate; &lt; 5% of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>Incidental finding during transurethral resection of prostate; &gt; 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor identified by needle biopsy (e.g., because of elevated PSA)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor confined within prostate (palpable or visible on TRUS)</td>
</tr>
<tr>
<td>T2a</td>
<td>Involves half of a lobe or less</td>
</tr>
<tr>
<td>T2b</td>
<td>Involves more than half of a lobe one lobe but not both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends through prostatic capsule, bladder neck or seminal capsule</td>
</tr>
<tr>
<td>T3a</td>
<td>Unilateral extracapsular extension</td>
</tr>
<tr>
<td>T3b</td>
<td>Bilateral extracapsular extension</td>
</tr>
<tr>
<td>T4</td>
<td>The tumor has spread or attached to tissues next to the prostate (other than the seminal vesicles)</td>
</tr>
<tr>
<td>T4a</td>
<td>The tumor has spread to the neck of the bladder, the external sphincter (muscles that help control urination), or the rectum</td>
</tr>
<tr>
<td>T4b</td>
<td>The tumor has spread to the floor and/or the wall of the pelvis</td>
</tr>
<tr>
<td>N0</td>
<td>Cancer has not spread to any lymph nodes</td>
</tr>
<tr>
<td>N1</td>
<td>Cancer has spread to a single regional lymph node (inside the pelvis) and is not larger than 2 centimeters</td>
</tr>
<tr>
<td>N2</td>
<td>Cancer has spread to one or more regional lymph nodes and is larger than 2 centimeters (2/3 inch), but not larger than 5 centimeters</td>
</tr>
<tr>
<td>N3</td>
<td>Cancer has spread to a lymph node and is larger than 5 centimeters</td>
</tr>
<tr>
<td>M0</td>
<td>The cancer has not metastasized (spread) beyond the regional lymph nodes</td>
</tr>
<tr>
<td>M1</td>
<td>The cancer has metastasized to distant lymph nodes (outside of the pelvis), bones, or other distant organs such as lungs, liver, or brain</td>
</tr>
<tr>
<td>TESTS</td>
<td>Very Low</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Clinical Stage = results from the digital rectal exam (DRE) and other imaging or tissue tests</td>
<td>T1c, and N0, M0</td>
</tr>
<tr>
<td>PSA = results from prostate specific antigen (PSA) blood test</td>
<td>&lt;10 ng/mL and density &lt;0.15 ng/mL/g</td>
</tr>
<tr>
<td>Biopsy Results = gleason score, number of cores positive for cancer, and the amount of cancer found in each core</td>
<td>Gleason score of 6 (usually 3+3) or less and less than 3 cores positive for cancer and no more than half of any core</td>
</tr>
</tbody>
</table>
Biopsy Pathological Reporting (Core, Specimen)

- In a prostate biopsy case, 10 to 14 cores are generally received.

- WRH practice…. 12 cores, submitted in 12 separate site-specific labeled containers.

- The reporting of prostate biopsies may be done at core and/or specimen level.

- The International Society of Urological Pathology (ISUP) recommends grading at the core level, if the cores are separately identified.

- Two biopsy case summaries are sometimes provided, individual core based summary and a specimen-level summary.
Histologic Types of Prostate Cancer

- Acinar adenocarcinoma, 95% cases
  - Atrophic
  - Pseudohyperplastic
  - Microcystic
  - Foamy gland
  - Mucinous (colloid)
  - Signet ring-like cell
  - Pleomorphic giant cell
  - Sarcomatoid
- Ductal adenocarcinoma
- Neuroendocrine tumors
  - Adenocarcinoma with neuroendocrine differentiation
  - Well-differentiated neuroendocrine tumor
  - Small-cell neuroendocrine carcinoma
  - Large cell neuroendocrine carcinoma

PROSTATE CANCER GRADING, CURRENT STATUS
How Are Gleason Scores Categorized in the Current Literature: An Analysis and Comparison of Articles Published in 2016-2017. Zhou AG<sup>1</sup>, Salles DC<sup>1</sup>, Samarska IV<sup>1</sup>, Epstein JI<sup>2</sup>.

Looked at how GSs were grouped worldwide looking at most of the published papers between 2016 - 2017.

Only 203/1393, 14.6% of the published articles were grouping GSs accurately.

It was also identified that the most common method of patient risk stratification is still based on the old method (NCCN).
63 years old
3+3=6
54 years old,
3+4=7
4 + 3 = 7
4 + 4 = 8/10
GLEASON GRADING

- A study conducted from 1959 through 1964 by the Veteran’s Affairs Cooperative Research Group (VACURG), which enrolled 270 men with prostate cancer. (J Urol. 1974;111:58–64.)

- Dr. Donald Gleason, the Chief of Pathology at the Veteran’s Hospital in Minnesota, created a grading system for prostate cancer based on its different histologic patterns.

- As most tumors typically had two histologic patterns, a score was created that added the two most common grade patterns in a tumor, with scores ranging from 2 to 10.

- The study demonstrated a progressive increase in cancer specific mortality with an increase in score.

- The five prognostic patterns were demonstrated by a simple diagram drawn by Dr. Gleason.
Grade 1: the glands form a compact mass;

Grade 2: the glands are more loosely aggregated, and some glands invade into the surrounding stroma.

Grade 3: distinct glands with surrounding stroma.

Grade 4: Irregular cribriform glands.

Grade 5: Solid sheets with comedo-necrosis, or single cells.

A few small cribriform glands are present in Gleason’s original pattern 2, large rounded cribriform glands are a major component of original pattern 3, and large irregular cribriform glands are the predominant component of pattern 4 along with fused glands.
Originally Gleason patterns 1 and 2 were frequently assigned.


Because of:

(i) Poor reproducibility even amongst experts;

(ii) Poor correlation with radical prostatectomy grade, with almost all cases showing higher grade and high stage at resection;

(iii) A diagnosis of Gleason score 2–4 may misguide clinicians and patients into believing that the patient has an indolent tumor.

As a consequence, the incidence of Gleason scores 2–4 on needle biopsy decreased to almost never seen in current practice.
In 2005 the first consensus conference of the International Society of Urologic Pathology (ISUP) was held.

Some of the issues related to Gleason Grading system were resolved.

The major changes made to the original grading system were to:

(i) Officially accept poorly formed glands as pattern 4,

(ii) Modify the rule for grading needle biopsies to report the most prevalent grade and the highest grade as opposed to the two most common grades,

(iii) Report different grades for each separate tumor nodule in a radical prostatectomy specimen,

(iv) Report tertiary patterns in radical prostatectomy specimens.
(v) To agree that Gleason patterns 1 and 2 should not be rendered in biopsy specimens,

(vi) Excluded cribriform glands in Gleason pattern 2 and tightened the criteria for cribriform pattern 3 so that only rare cribriform glands would be graded as pattern 3,

(vii) Recommended reporting different Gleason scores for different positive cores, as long as the cores were designated according to the location within the prostate.
Unresolved issues

Some issues were still not resolved in 2005 ISUP consensus recommendations due to the limited data regarding outcome.

For example,

• small cribriform glands were retained as pattern 3,

• No agreement reached on grading mucinous adenocarcinoma of the prostate or glomeruloid patterns,

• No recommendations regarding the reporting or grading of intraductal carcinoma.
MODIFICATIONS TO THE GLEASON SYSTEM IN 2014

To address unresolved issues from 2005, in November 2014, a conference was held in Chicago, IL that included experts in prostate cancer pathology from 17 different countries, clinical specialists in the fields of urology, radiation, and medical oncology.

The participants used published material and personal experience and voted on issues relating to the grading of:

- Mucinous carcinoma,
- Glomeruloid pattern and small cribriform glands,
- Intraductal carcinoma
- New proposed Group grading system.
Mucinous carcinoma, Glomeruloid and cribriform glands

It was agreed upon that mucinous carcinomas should be graded based on their underlying architectural pattern as many studies have demonstrated a relatively favorable outcome in mucinous prostate cancer.

Glomeruloid and Small round cribriform pattern that was still designated as Gleason pattern 3 in the 2005 consensus conference, was included in pattern 4.

Glomeruloid pattern is considered an early form of the cribriform pattern.

In 2009, Lotan et al. demonstrated that 84% of cases with glomeruloid glands were associated with Gleason pattern 4 or higher cancer.

All cribriform patterns were assigned pattern 4, as studies have demonstrated that any cribriform morphology imparted aggressive behavior to prostate cancer.
Intraductal carcinoma

• It was decided not to grade intraductal carcinoma, but note its presence and that it is typically associated with the presence of more aggressive cancer.

• This typically represents extension of high grade cancer into ducts.

• In a minority of cases, it represents a precursor lesion that may either not have associated invasive carcinoma or have lower grade cancer,

• So grading the intraductal carcinoma would over-grade the lesions and give the patients a worse prognosis than expected.
Tertiary grade on needle core biopsy

In contrast to the original Gleason grading system, it is now recommended that on a needle core biopsy both the most common and highest grade are added together for the Gleason score.

Example,
60 % Gleason pattern 3,
35 % Gleason pattern 4,
and 5 % Gleason pattern 5,
Gleason score would be 3 + 5 = 8.

• Needle core biopsy is an imperfect, non-targeted, random sampling of the prostate gland.

• Thus any amount of high-grade tumor sampled on needle biopsy most likely indicates a more significant amount of high-grade tumor within the prostate.

In all specimens, in the setting of high-grade cancer, one should not report a lower grade if it occupies less than 5 % of the total tumor.

example,
98 % Gleason pattern 4
and 2 % Gleason pattern 3,
the Gleason score would be reported as 4 + 4 = 8

The issue of tertiary grade patterns

- Tertiary patterns are not reported on needle biopsies, only the most prevalent and the highest-grade patterns are reported.

- In radical prostatectomy specimens, if the Gleason pattern 5 comprises $<$5% of tumor nodule, it is recorded as a tertiary grade.

For example, in a needle biopsy specimen with:
60% of pattern 3,
38% of pattern 4, and
2% of pattern 5
will be reported as 3+5=8

In a prostatectomy specimen, the same percentages of different patterns will be graded as 3+4=7 with tertiary pattern 5.
Reporting %age of pattern 4 in Gleason score 7 cancers

Another major recommendation from the 2014 consensus conference.

• It is particularly important in Gleason score 3+4=7 disease on needle biopsy as the cancers with minimal (<5%) versus more extensive (40–50%) pattern 4 may be treated differently;

• In the setting of minimal pattern 4 some men depending on age, and other factors may still be candidates for active surveillance,

• whereas those with increased pattern 4 may be recommended for definitive therapy.
Grade Grouping ---- A new grading system
A new grading system

In 2013, a new grading system was proposed by the group from Johns Hopkins Hospital which was accepted in 2014 consensus conference of ISUP.

The grading system includes five distinct Grade Groups based on the modified Gleason score groups.

Grade Group 1 = Gleason score \( \leq 6 \),
Grade Group 2 = Gleason score \( 7(3 + 4) \),
Grade Group 3 = Gleason score \( 7(4 + 3) \),
Grade Group 4 = Gleason score \( 8(4 + 4, 3+5, 5+3) \)
Grade Group 5 = Gleason scores 9 and 10.

A multi-institutional study validated the new grading system on 20,845 radical prostatectomy cases with a mean follow-up period of 3 years (Ref).

The 5-year biochemical risk-free survivals for the 5 Grade Groups based on radical prostatectomy grade were 96, 88, 63, 48, and 26 %, respectively.

These Grade Groups were shown to be more accurate in predicting progression than the Gleason risk stratification groups \((\leq 6, 7, 8-10)\).
Newly proposed grade groups in prostate cancer

<table>
<thead>
<tr>
<th>Grade group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade group 1</td>
<td>Gleason score ≤ 6</td>
</tr>
<tr>
<td>Grade group 2</td>
<td>Gleason score 3 + 4 = 7</td>
</tr>
<tr>
<td>Grade group 3</td>
<td>Gleason score 4 + 3 = 7</td>
</tr>
<tr>
<td>Grade group 4</td>
<td>Gleason score 8 (4 + 4, 3 + 5, 5 + 3)</td>
</tr>
<tr>
<td>Grade group 5</td>
<td>Gleason score 9–10 (4 + 5, 5 + 4, 5 + 5)</td>
</tr>
</tbody>
</table>
A. Gleason score 3 + 3 = 6 (Grade Group 1).

B. Gleason score 3 + 4 = 7 (Grade Group 2) with minor component of cribriform glands.

C. Gleason score 4 + 4 = 8 (Grade Group 4) with irregular cribriform glands.

D. Gleason score 4 + 4 = 8 (Grade Group 4) with fused glands with cytoplasmic vacuoles.

e. Gleason score 4 + 4 = 8 (Grade Group 4) with glomeruloid glands.

f. Gleason score 4 + 4 = 8 (Grade Group 4) with poorly-formed glands.
A. Gleason score 5 + 5 = 10 (Grade Group 5) with solid sheets of cells.

B. Gleason score 5 + 5 = 10 (Grade Group 5) with cords of cells.

C. Gleason score 5 + 5 = 10 (Grade Group 5) with individual cells.

D. Gleason score 5 + 4 = 9 (Grade Group 5) with cribriform glands, some with necrosis.

E. Intraductal carcinoma with necrosis (left), surrounded by basal cells highlighted by p63 and high molecular weight cytokeratin (right) and positive for racemase.

F. Mucinous adenocarcinoma Gleason score 3 + 4 = 7 (Grade Group 2) with individual well-formed glands and minor component of cribriform glands floating in extracellular mucin.
RATIONALE FOR THE NEW GRADING SYSTEM

The lowest score reported in prostate biopsy and radical prostatectomy specimens for the most part is 6 (3+3).

This was confusing as logically it seemed to patients that they had cancer in the mid-range of aggressiveness on a scale of 2 to 10 scores.

There was a suggestion to replace Gleason score 3+3=6 disease with IDLE (indolent lesion of epithelial origin) to avoid fear and overtreatment,

However, studies have shown that Gleason pattern 3 in the setting of surrounding Gleason pattern 4 may have metastatic potential indicating that Gleason pattern 3 should be classified as cancer.

Rather than changing “Gleason score 6” to a non-cancerous diagnosis, there was a need to change the way that Gleason score 6 cancer is reported to reflect that it is the lowest grade with an excellent prognosis. Which was done in new grade grouping.
Continued:

Of particular importance, the new grading system separates cancers with Gleason score 7 into Grade Groups 2 and 3.

In urology the D’Amico/ NCCN risk classification system includes Gleason score 7 within the intermediate risk category without recognizing the distinction between 3+4=7 and 4+3=7.

Similarly, the D’Amico high-risk group lumps together Gleason scores 8–10, despite Gleason scores 9–10 having twice as worse a prognosis compared to Gleason score 8(Ref).
The Grade Groups showed similar prognostic curves on biopsy in men treated with radiation +/- hormonal therapy as well as radical prostatectomy.

Using this new system, patients could be reassured that they have a Grade Group 1 tumor on biopsy that is the lowest grade tumor possible, which in most cases can be followed with active surveillance.

Follow-up is still needed as in approximately 20% of cases, there is un-sampled higher grade cancer.

As this new grading system is simpler and more accurately reflects prostate cancer biology, it is recommended using it in conjunction with Gleason grading.

For example:
Gleason score 3 + 3 = 6 (Grade Group 1)

This new grading system has been accepted by the World Health Organization (WHO) for the 2016 edition of Pathology and Genetics: Tumours of the Urinary System and Male Genital Organs [Ref].
Limitations of the new system:

Despite being simple, useful in counselling and prognosticating, it has few deficiencies.

- In grade group 4 (Gleason score $4 + 4 = 8$, $3 + 5 = 8$, $5 + 3 = 8$), there is now enough evidence to suggest that the prognosis of $4 + 4 = 8$ is better than $3 + 5 = 8$ and $5 + 3 = 8$, but are still grouped together.

- It is a point worth considering for the future discussions.

- Some of the recent evidence suggests that prognosis of Gleason score $5 + 3 = 8$ is similar to GS 9.

- Tertiary pattern, percentage of the worse pattern in a given Gleason pattern, does play a significant role in the prognosis;

- Further guidelines on this aspect would be of help especially when we call these grade groups as prognostic grade groups.
Ok...Just write "Funny looking cells in pink and violet. Correlate clinically."
Quantitation of Tumor

• Studies have shown prostate cancer volume is a prognostic factor,

• The estimated percentage of prostatic tissue involved by tumor and/or the linear millimeters of the tumor needs to be reported.

• Reporting of the positive core with the greatest percentage of tumor is an option since in some active surveillance (AS) protocols, the presence of any cores with >50% involvement is an exclusion criterion.

• The designation of the percentage of cancer tissue in transurethral samples is important to determine the clinical stage.
Local Invasion in Needle Biopsies

- Peri-prostatic fat involvement indicates that the tumor is at least pT3a in the TNM system.
- If seminal vesicle tissue is present and involved by tumor, it suggests that the tumor may be pT3b.
- It is very unusual to see EPE in the needle biopsy and still meet all other criteria for AS.
- EPE is associated with increased risks of BCR and positive margins at RP.
Perineural invasion has been found to be an independent risk factor for predicting an adverse outcome in patients treated with external beam radiation,

but not for patients treated with brachytherapy or radical prostatectomy.
Reporting of Prostatic Intraepithelial Neoplasia (PIN)

- The diagnostic term prostatic intraepithelial neoplasia (PIN) refers to high-grade PIN.

- Low-grade PIN is not reported.

- The presence of an isolated PIN (PIN in the absence of carcinoma) needs to be reported in biopsy specimens, especially if more than 1 site is involved.

- The reporting of PIN in biopsies with carcinoma is considered optional.

- More recent data suggests that if high-grade PIN is present in 2 or more sites, there is an increased risk of detecting carcinoma in subsequent biopsies.

- The reporting of high-grade PIN in prostatectomy specimens is optional.
Atypical Small Acinar Proliferation (ASAP)

Small atypical glandular focus in biopsy that is quantitatively and/or qualitatively insufficient to confidently diagnose carcinoma.
Atypical Small Acinar Proliferation (ASAP)

- Diagnosed in about 5% of prostate biopsies, varies even among experts.

- Not a specific diagnosis, mostly represents under sampled carcinoma,

- Also includes a collection of cancer mimics.

- Diagnosis of isolated ASAP is an indication for repeat biopsy, usually within 3 to 12 months.

- Cancer is detected in subsequent biopsies in about 35% to 60% of cases. (J Urol. 2006;175:820-834.)

- The likelihood of detecting cancer is higher when there is concomitant multifocal PIN. (Am J Surg Pathol. 2010;34:169-77).
Seminal Vesicle Invasion

- Seminal vesicle invasion is a significant adverse prognostic factor associated with increased risk of PSA recurrence.
- There are different mechanisms of seminal vesicle invasion including:
  1. direct invasion of the seminal vesicle from the base of the prostate;
  2. extraprostatic extension with subsequent invasion of seminal vesicle walls;
  3. involvement along the ejaculatory duct into the seminal vesicle; and
  4. discontinuous involvement, which likely represents vascular spread.
Margins

• Margin positivity is a significant adverse prognostic factor.

• To properly evaluate, the entire surface of the prostate is inked.

• The apical and bladder neck surgical margins are submitted entirely for examination.

• The specific location and the extent of margin positivity is important to report.

• Studies suggest that the Gleason grade or score at a site of margin positivity is correlated with biochemical recurrence.

• The presence of any pattern 4 or 5 in tumor at a margin doubles the risk of PSA recurrence compared to only Gleason pattern 3 at margin.
Positive inked margin
Summary;

- Complete pathological report plays a central role in risk stratification of patients with prostate cancer.

- The new grade group system needs to be regularly incorporated in pathology reports.

- The new grade group system is simple, easy to adopt and useful in counselling the patients.

- Treatment options can be tailored according to the grade groups.

- It has the potential to avoid the fear in grade group 1 patients who will be in a position to choose wisely; it would also help in avoiding the overtreatment.

- This system still have certain limitations that need to be looked in to.
References:


Thank you