PROSTATE CANCER

CHAPTER 3

Pathology

Abbreviations and Acronyms

%	= Percentage
+ve	=Positive
ADH	= Antidiuretic Hormone
ASAP	= Atypical Small Acinar Proliferation
BN	=Bladder Neck
CLL	= Chronic Lymphocytic Leukemia
DRE	=Digital Rectal Examination
EPE	= Extraprostatic extension
GS	= Gleason Score
HG	= High Grade
HT	=Hormonal Therapy
LG	= Low Grade
IDC-P	= Intraductal Carcinoma Of The Prostate
NE	= Neuroendocrine
No	= Number
PCa	=Prostate Cancer
PIN	= Prostatic Intraepithelial Neoplasia
PNI	= Perineural Invasion
PSM	= Positive Surgical Margin
Pts	= Patients
Px	=Prognosis
RP	= Radical Prostatectomy
RT	= Radiotherapy
SCC	= Squamous cell carcinoma
W/U	= Work Up

Diagnosis, management and follow-up of patients with PCa are highly dependent on a combination of laboratory, clinical and pathologic factors[1-4]. Pathologic factors include prostate biopsies and radical prostatectomy specimen. The biopsy GS is the most significant predictor of pathologic outcome at RP[1, 5-11].

Approximately, 70% of cases of PCa originate in the peripheral zone, while 10–20% originate in the transition zone, and 5–10% in the central zone[12]. So, extraprostatic extension mainly occurs posteriorly and posterolaterally, due to the location of most prostate cancers[13].Prostate adenocarcinoma is the most common form of PCa. In fact, over 95% of the PCa are adenocarcinomas[9]. Adenocarcinoma of the prostate is multifocal in more than 85% of cases[13, 14].

High grade prostatic intraepithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP) are thought to be precursor lesions for PCa[12, 13]. In other words, men found to have either lesion may be at an increased risk of PCa[12, 13]. Prostatic intraepithelial neoplasia (PIN) consists of architecturally benign prostatic acini or ducts lined by cytologically atypical cells and is classified as low-grade and high-grade neoplasias[13].

Clinical significance and recommended approaches to LG-PIN, HG-PIN, PIN in the TURP specimen and ASAP have been summarized in table-1 and figure 1-4. - Prostate biopsy reports that need special attention even when there is no reported cancer have been summarized in table 1. Comparison of recommended attitude for pathologists toward LG-PIN and HG-PIN13 has been shown in figure 1. Recommended strategy regarding repeat biopsy within one year in patients with HG-PIN which had initial extended core sampling has been illustrated in figure 2. Recommended strategy toward HG-PIN found in TURP specimens has been shown in figure 3. Recommended attitude toward further evaluation of ASAP has been summarized in figure 4.

Table 1- Prostate biopsy reports that need special attention even when there is no reported cancer [13, 15-17]

Pathology	Remarks
HG-PIN	• Precursor of intermediate and high grade prostate cancer • Does not increase PSA
ASAP	42-49% of them will show adenocarcinoma in re-biopsy specimens

Figure 1- Comparison of recommended attitude for pathologists toward LG-PIN and HG-PIN[13]

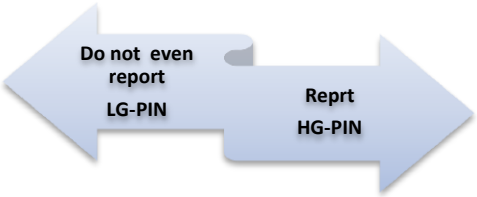


Figure 2- Recommended strategy regarding repeat biopsy within one year in patients with HG-PIN which had initial extended core sampling [13, 18-21]

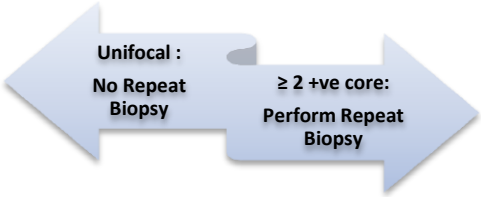
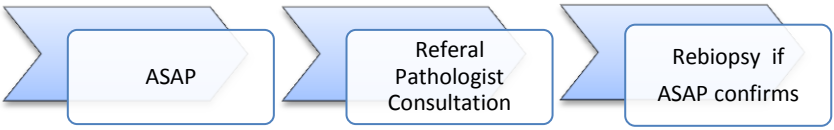


Figure 3 -Recommended strategy toward HG- PIN found in TURP specimens[1]

Figure 4 - Recommended attitude toward further evaluation of ASAP[13]



Gleason grade is the current standard for grading adenocarcinoma of the prostate on biopsy and surgical specimens[13, 22]. The Gleason system is based on the glandular pattern of the tumor as identified at relatively low magnification[13].Gleason score or Gleason sum is obtained by adding the primary and secondary grades together[12]. As Gleason grades range from 1 to 5, Gleason scores or sums thus ranges from 2 to 10[12], while 2 is the least aggressive score and 10 is the worst one[22].

Most patients will likely have Gleason score 6 or 7 disease, reflecting the most common current grading category[23]. Almost half of tumors graded Gleason score 6 at biopsy are Gleason score 7 at surgery[24]. Upgraded Gleason score 6 to 7 tumors have outcomes similar to those of genuine Gleason score 7 cancer[24]. In fact, GS 7 is now the most commonly assigned score in many settings[1, 25, 26]. Some of prominent items in this regard have been summarized in table 2-6.

Table 2- Items that should be included in prostate biopsy pathology report[1, 13]

Items	Gleason Pattern
	No of +ve cores
	One of -% of Each involved core -Total % of cancer - Total milimeter of cancer among all cores
	Presence or absence of perineural invasion

Table 3– Gleason Grades most typical findings[1, 12, 13]

Gleason grade	Typical findings
1-2	Uniform, medium size closely packed glands
3	Variable size, closely packed glands
4	Incomplete gland formation, Cribriform glands
5	Single infiltrating cells, Cords, Sheaths

Table 4- Calculation of Gleason Score of biopsy specimen in different scenarios[1, 13]

Scenario	Remarks	Primary pattern	Secondary pattern
1 pattern		Visible pattern	The same
2 patterns		Most common pattern	Second most common pattern
2 patterns **2nd = LG & < 5%**	Ignore the LG Pattern	HG pattern	The same
2 patterns **2nd = HG & < 5%**	Should include HG pattern	Most common pattern	The HG pattern
3 patterns		Most common pattern	Pattern with highest grade

Table 5- Gleason score and related degrees of differentiation [12, 27]

Gleason sum*	Differentiation
2-4	Well differentiated
5-6	Moderately differentiated
8-10	Poorly differentiated

*Historically Gleason score 7 have sometimes been grouped with moderately differentiated tumors and at the other times with poorly differentiated tumors. One point that needs to be clarified is that the primary Gleason grade is perhaps the most

important with respect to placing patients in prognostic groups[12].In fact, patents with Gleason sum of 7 who have a primary (most common pattern) Gleason grade of 4(4+3) tend to have a worse prognosis than those who have primary Gleason grade of 3 (3+4)[12].

Table 6– Situations that need special attention in assessing biopsy specimen[1, 13]

Scenario	Remarks
LG PIN	Should not be reported by pathologist
GS 1+1,1+2,2+2 on needle biopsy	Should rarely if ever be made on a needle biopsy, because these patterns are rare and only infrequently confirm in subsequent RP specimen report
GS after castration	• Pathologist should not report a GS if there is any pathologic clues to these treatments • If other areas of the tumor do not show a pronounced hormone effect, these areas can be Gleason graded
Biopsy after RT	• BPH may mimic PCa • When only irradiated cancer is seen, the case may be signed out as ''adenocarcinoma with profound treatment effect'' and not graded • When usual-type adenocarcinoma is only present after therapy, the cancer is graded • The biochemical recurrence-free and distant failure rates for patients having only cancer with profound treatment effect are similar to the rates for patients with benign biopsies, as opposed to patients with gradable cancer. Said another way, the presence or absence of gradable cancer in a biopsy after radiation therapy is a major indicator of clinical outcome
Adenosis	• It is adenomatous hyperplasia • Its appearance may mimic cancer • It is not associated with cancer
Finasteride	Does not have any effect on pathology

Intraductal carcinoma of the prostate (IDC-P) is rare significant finding in biopsy specimen and should not be mistaken with PIN (table-7).

Table 7- Most important remarks regarding Intraductal carcinoma of the prostate[1, 13, 28-30]

- Intraductal carcinoma is different than HG-PIN.
- In most cases IDC-P represents intraductal spread of carcinoma.
- Intraductal carcinoma is rarely seen in the absence of invasive cancer.
- In contrast to HG- PIN, intraductal carcinoma is rare in areas away from carcinoma.
- Large number of patients have invasive cancer with GS >7 and pT3 disease at subsequent RP.
- Some experts recommend definitive therapy when intraductal carcinoma is diagnosed on needle biopsy.
- Consideration should be given to aggressively treating patients with IDC-P on biopsy, even in the absence of documented infiltrating cancer.

Over 95% of the PCa are adenocarcinomas[12]. Most adenocarcinomas that we encounter in our everyday practice are ordinary or acinar adenomas[12, 13].Some high lights about other subtypes of adenocarcinoma and also some other prostatic neoplasia have been summarize in table -8.

Table 8 –Different neoplasms of prostate gland[1, 12,13,31,32]

Neoplasm	Remarks
Ordinary adenocarcinoma	• Ordinary=Conventional=Usual= Acinar • 95% of cases
Mucinous adenocarcinoma	• Rare • Behaves like ordinary
Prostate duct adenocarcinoma	• DRE may be normal • PSA may be normal • Most have and aggressive course • They should be regarded as GS=8 • Most are at advanced stage at time of diagnosis
Well differentiated NE tumors	• Carcinoid tumors • Mainly as prostatic adenocarcinoma with focal NE differentiation • Do not cause carcinoid syndrome
Aggressive NE tumors	• Small Cell Carcinoma • Not graded • Average survival < 1 year • Very uncommon • Some of them (10%) cause paraneoplastic syndromes like Cushing syn, hypercalcemia, excess ADH & etc. • A high percentage of them evolve from prostatic adenocarcinoma subsequent to HT • Pure cases do not increase PSA level • There is no difference in prognosis between patients with pure small cell carcinoma and those with mixed glandular and small cell carcinomas

Primary urothelial carcinoma of prostate	• 1-4% of all prostate cancers • Most common primary prostate tumor after adenocarcinoma • >50% present with stage T3 or T4 • 20% have metastatic disease at time of presentatation • Can cause lytic bone lesions
Primary SCC of prostate	• Rare • Poor Px • Can cause osteolytic bone lesions
Sarcomatoid carcinoma	Poor Px
Rhabdomyosarcoma	• Rare • Most common mesenchymal tumor of prostate in childhood
Leiomyosarcoma	• Rare • In adulthood
Primary lymphoma	Secondary is more common
Leukemic involvement of prostate	CLL is the most common one
Other metastatic tumors	Rare
Others primary tumors	Rare

Pathology report of radical prostatectomy specimen is a very important piece of information regarding further follow up and management of the patient. Items that should be included in radical prostatectomy report by pathologist, pathologic staging and significance of PNI have been summarized in table 9-11 and figure 5.

Table9- Items that should be included in RP report by pathologist[13, 33-36]

Parameter	Remarks
Treatment related change	Pathologic changes following RT or HT
GS	• Primary + secondary patterns • Tertiary pattern*
Location	Location of dominant tumor mass
Tumor volume	Is not an independent prognostic factor
Spread of tumor	• EPE • SV invasion
Perineural invasion	Dose not worsen Px
Vascular invasion	Increases the risk of recurrence after RP
Pathologic stage	• pT stage • pN stage

*It is recommended that in RP specimens, the routine Gleason sum, consisting of the most prevalent and the second most prevalent patterns, be assigned along with a note stating that there is a tertiary high-grade pattern[8]. Some authors like Epstein consider 3rd most prevalent pattern as secondary pattern if it has the highest grade and occupies > 5% of tumor volume[33] and consider it as tertiary pattern only when it is < 5% of total tumor volume in RP specimen[33].

Table 10 –T staging of radical prostatectomy specimen[1, 13]

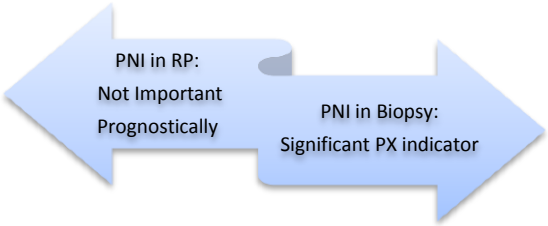
T-Stage	Definition	Subtypes	Tumor extent
pT2*	Organ confined	pT2a	≤one-half of one side
		pT2b	>one-half of side
		pT2c	Bilateral
pT3	EPE	pT3a	-Extraprostatic extension -Microscopic invasion of BN
		pT3b	SV invasion
pT4	Invasion of bladder neck, rectum, levator muscles, and/or pelvic wall		

*most pathologists now agree that substaging of pT2 holds limit clinical value and that the next TNM staging update should consider obviating the need to include this information[1, 37]

Table 11- N staging of radical prostatectomy associated lymphadenectomy[13]

N-Stages	Definition
pNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional node(s)

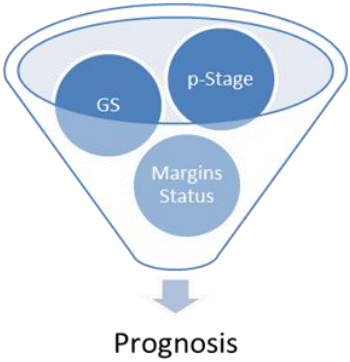
Table12- Comparison of PNI significance in biopsy and radical prostatectomy specimens[13]



Gleason score, RP margins and pathologic stage are the main determinants of prognosis after RP (Figure-5). Tumor volume correlates well with GS and pathologic stage, however, it is not an independent predictor of post radical prostatectomy progression once the above mentioned factors have been considered[13, 38]. Another issue is the impact of positive surgical margins. In fact, although positive surgical margins are associated with disease recurrence after RP, only approximately 50% of such patients will progress[13]. The risk group of patients seems to be a significant factor to predict this progression. In a study done in Princes Margaret Hospital, the biochemical progression-free survival was 94.9%, 83% and 57.1% for low risk, intermediate risk and high risk disease with positive surgical margins [39]. In other words, positive surgical margins are an independent predictor of biochemical progression in patients with intermediate and high risk prostate cancer and patients with low risk disease have a favorable long-term outcome

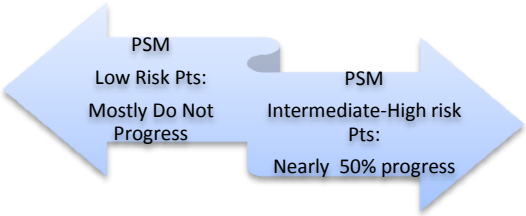
regardless of margin status [39, 40] (Figure-6) .It is noteworthy to emphasize that intraprostatic incision at the time of RP behaves like positive surgical margins and warrants the same management strategies[13]. Summary of prognosis discussion has been shown in the figure 5.

Figure 5-Most important items to predict cancer-specific prognosis following RP



*Positive surgical margins seem to have a more considerable role in intermediate and high risk patients, even though roughly 50% of these patients do not progress in future.

Figure 6- Comparison of PSM after RP in different risk groups



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