Prostate Core Needle Biopsy Histopathology Reporting Guide

Part 2 - Specimen Level Reporting

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED.

FOR *EACH* SPECIMEN - COMPLETE THE FOLLOWING:

SPECIMEN ID:

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 1)

- ◯ No evidence of primary tumour
- ☐ Adenocarcinoma (Acinar, usual type)
- ☐ Other *(specify)*

HISTOLOGICAL GRADE (Note 2)

Gleason score

Primary pattern/grade

◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5

Highest remaining pattern/grade

◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5

◯ Indeterminate *(specify reason)*

International Society of Urological Pathology (ISUP) Grade (Grade Group)

- ◯ ISUP Grade (Grade Group) 1 (Gleason score ≤6)
- ◯ ISUP Grade (Grade Group) 2 (Gleason score 3+4=7)
- ◯ ISUP Grade (Grade Group) 3 (Gleason score 4+3=7)
- ◯ ISUP Grade (Grade Group) 4 (Gleason score 8)
- ◯ ISUP Grade (Grade Group) 5 (Gleason score 9-10)
- ◯ Indeterminate *(specify reason)*

Percentage Gleason pattern 4/5 *(applicable for Gleason scores ≥7)*

% ◯ Not identified

TUMOUR EXTENT (Note 3)

Number of positive cores/total number of cores /

AND

Length of tissue involved by carcinoma mm

OR

Linear extent of prostatic tissue involved by carcinoma %

PERINEURAL INVASION (Note 4)

◯ Present ◯ Not identified

SEMINAL VESICLE/EJACULATORY DUCT INVASION (Note 5)

◯ Present ◯ Not identified

LYMPHOVASCULAR INVASION (Note 6)

◯ Present ◯ Not identified

EXTRAPROSTATIC EXTENSION (EPE) (Note 7)

◯ Present ◯ Not identified

Location (select all that apply)

- ☐ Right base
- ☐ Right mid
- ☐ Right apex
- ☐ Left base
- ☐ Left mid
- ☐ Left apex
- ☐ Other *(specify)*

INTRADUCTAL CARCINOMA OF PROSTATE (Note 8)

◯ Present ◯ Not identified

COEXISTENT PATHOLOGY (Note 9)

- ◯ None identified
- ◯ Present *(specify)*

Version 1.1 Published August 2017 ISBN: 978-1-925687-10-1

Scope

The dataset has been developed for the examination of prostate core needle biopsies. The elements and associated commentary apply to invasive carcinomas of the prostate gland. Urothelial carcinomas arising in the bladder or urethra are dealt with in a separate dataset, while urothelial carcinomas arising in the prostate are included in this dataset.

Note 1 - Histological tumour type (Required)

Reason/Evidentiary Support

The vast majority (>95%) of prostate cancers are acinar adenocarcinomas.[1] Other types of carcinoma are rarer but must be recorded if present, since some variants, such as ductal adenocarcinoma, small cell carcinoma, sarcomatoid carcinoma and urothelial-type adenocarcinoma, have a significantly poorer prognosis.[1-6] The tumour type should be assigned in line with the 2016 World Health Organisation (WHO) classification and mixtures of different types should be indicated.[1] Subtypes of prostate carcinoma are often identified in combination with acinar type carcinoma, and in such cases the tumour type should be classified according to the subtype.

WHO classification of tumours of the prostate[a1]

Descriptor	ICD-O codes
Epithelial tumours	
Glandular neoplasms	
Acinar adenocarcinoma	8140/3
Atrophic	
Pseudohyperplastic	
Microcystic	
Foamy gland	
Mucinous (colloid)	8480/3
Signet ring-like cell	8490/3
Pleomorphic giant cell	
Sarcomatoid	8572/3
Prostatic intraepithelial neoplasia, high-grade	8148/2
Intraductal carcinoma	8500/2
Ductal adenocarcinoma	8500/3
Cribiform	8201/3
Papillary	8260/3
Solid	8230/3
Urothelial carcinoma	8120/3
Squamous neoplasms	
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Basal cell carcinoma	8147/3
Neuroendocrine tumours	
Adenocarcinoma with neuroendocrine differentiation	8574/3
Well-differentiated neuroendocrine tumour	8240/3
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3

a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.

Urothelial carcinomas arising in the urinary bladder or urethra are dealt with in separate datasets; however, those rare urothelial carcinomas arising within the prostate are included in this dataset. Information on histological tumour type may be recorded at a specimen level or at a case level depending on local practice. The response type “No evidence of primary tumour” should only be used if specimen level reporting is utilised.

Back

Note 2 - Histological grade (Required and Recommended)

Reason/Evidentiary Support

The Gleason grading system is the foundation of grading for prostatic adenocarcinoma. The Gleason score is traditionally obtained by adding the two predominant Gleason patterns or doubling the pattern in cases with uniform grade. This was modified in the International Society of Urological Pathology (ISUP) 2005 revision by always including the highest grade in the Gleason score of needle biopsies, regardless of its amount.[7] At a subsequent ISUP consensus conference in 2014, the Gleason system was further modified and many of the decisions taken at this meeting have been included in the 4th edition of the WHO classification. It was decided that Gleason pattern 4 should include fused or poorly formed glands, glomerulations and all cribriform patterns of acinar adenocarcinoma. A grouping of the Gleason scores into 5 grade categories was proposed and this was endorsed by the ISUP Council (March 2015). Over the past decades Gleason scores below 6 have become less commonly used, especially on needle biopsies. There is also an understanding that Gleason score 7 tumours have a worse prognosis if there is a predominant pattern 4 (4+3) than if pattern 3 dominates (3+4).

Both the Gleason score and the ISUP grade (Grade group) should always be reported for the sake of clarity.

The ISUP consensus conference also recommended that the percentage of Gleason pattern 4 be reported in cases with ISUP grades 2 or 3. The rationale for this is to indicate if the tumour is bordering on the lower or higher ends of Gleason score 7. In some jurisdictions, Gleason score 7 tumours with ≤10% pattern 4 are considered for active surveillance.[8] The percentage of Gleason pattern 4 and 5 is reported by some pathologists[9] but this was not endorsed by the WHO classification working group. This element is thus optional.

Depending on local practice, the different elements of grade data may be reported on either core or specimen level or as a composite (global) grade based on all cancer present in the biopsy cores or a combination of both.

The grade groups and associated definitions are outlined in Table 1.

Both the Gleason score and the ISUP grade (Grade group) should always be reported for the sake of clarity.

Table 1: ISUP grading system, core/needle biopsies and transurethral resection of the prostate (TURP) specimens

ISUP grade (Grade group)	Gleason score	Definition
Grade 1	2-6	Only individual discrete well-formed glands
Grade 2	3+4=7	Predominantly well-formed glands with lesser component (*) of poorly- formed/fused/cribriform glands
Grade 3	4+3=7	Predominantly poorly-formed/fused/cribriform glands with lesser component (**) of well-formed glands
Grade 4	4+4=8	Only poorly-formed/fused/cribriform glands
	3+5=8	Predominantly well-formed glands and lesser component (*) lacking glands (or with necrosis)
	5+3=8	Predominantly lacking glands (or with necrosis) and lesser component (**) of well-formed glands
Grade 5	9-10	Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

* Any component of the high-grade pattern (i.e. even if less than 5%) is included in the grade.
** The low-grade pattern is included in the grade only if it is at least 5%.

⬆ **Back**

Note 3 - Tumour extent (Required)

Reason/Evidentiary Support

Number of biopsy cores positive for cancer and linear extent of cancer in the cores correlate with tumour volume, postoperative stage and outcome.[10-14] Number of positive cores should be reported but may be difficult to determine because of fragmentation when multiple cores have been submitted together. The number of positive cores should not be greater than the number of cores taken (as specified in "Clinical Information"). Site specific labelling and single core submission facilitates the assessment of cancer extent.[15] Linear extent should be reported and may be recorded either as millimetres cancer length or % cancer in each core or as a composite measure of cancer involvement in all cores.[16] The methods for reporting of discontinuous cancer remain controversial. Whether intervening benign tissue is included or subtracted from the extent measurement may

determine eligibility for active surveillance. A patient with ISUP grade 1 (Gleason score 3+3=6) cancer in no more than 3 cores may be a candidate for active surveillance. In some protocols, if a positive core is greater than 50% involved by tumour, a patient would be ineligible for active surveillance.[17] In such a case it is recommended that the tumour extent of a discontinuous cancer should be reported by both including and subtracting the intervening benign tissue, e.g. In a 20 mm core there are discontinuous foci of cancer ISUP grade 1 cancer spanning a distance of 12 mm (60% linear extent) and measuring 1+1 mm (10% linear extent).[17]

Back

Note 4 - Perineural invasion (Recommended)

Reason/Evidentiary Support

The significance of perineural invasion in prostate core biopsy specimens is uncertain. Some studies show a correlation with extraprostatic extension (EPE) in the corresponding radical prostatectomy specimens or an association with adverse outcome in patients treated with radical prostatectomy or external beam radiation.[18-20,21-23] Other investigators have questioned prognostic value of biopsy perineural invasion in univariate or multivariate analyses.[24-27] A systematic review of the literature concluded that the weight of evidence suggested that in clinically localised disease perineural invasion was a significant prognostic factor for EPE and subsequent local recurrence.[28] In advanced disease perineural invasion is common and probably not of prognostic significance. It should also be noted that nerves are not necessarily present in biopsy material, therefore it is not always possible to assess the possibility of perineural invasion.

Back

Note 5 - Seminal vesicle/ejaculatory duct invasion (Recommended)

Reason/Evidentiary Support

Seminal vesicle invasion (SVI) is rarely identified in needle biopsies cores, hence its absence does not need to be explicitly stated. However, if seminal vesicle/ejaculatory duct invasion is present it should be recorded and the following comments apply.

SVI is defined as involvement of the muscular wall of the extraprostatic portion of the seminal vesicle.[29] If possible seminal vesicle tissue is present (either unintentionally or intentionally, as in a targeted biopsy) and involved by carcinoma, this may be significant since it indicates that the tumour could be pT3b in the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Staging system.[30,31] However, assessment of SVI is problematic in needle biopsy specimens since it is impossible to reliably distinguish between extraprostatic seminal vesicle and intraprostatic seminal vesicle or ejaculatory duct tissue, therefore it is important not to over interpret invasion of the latter two structures as SVI since their involvement by tumour does not constitute pT3b disease. Unless one is dealing with a targeted seminal vesicle biopsy, it is recommended to report tumour involvement of such structures in a needle core biopsy as “seminal vesicle/ejaculatory duct invasion” rather than as SVI.

Back

Note 6 - Lymphovascular invasion (Recommended)

Reason/Evidentiary Support

Lymphovascular invasion (LVI) is rarely identified in needle biopsies cores, hence its absence does not need to be explicitly stated. However, if LVI is present it should be recorded and the following comments apply.

Invasion of lymphatic or blood vessels (i.e. thin-walled endothelial-lined spaces) is uncommonly identified in needle core biopsy specimens and there is little published data on the significance of LVI specifically relating to prostate core biopsies. However, there is good evidence that LVI is a significant independent prognostic indicator of increased risk of recurrence post radical prostatectomy;[32-35] therefore, if LVI is identified in a needle core it may well be significant and its presence should be recorded. The presence of LVI does not affect assignment of the AJCC/UICC T category.

Back

Note 7 - Extraprostatic extension (Required and Recommended)

Reason/Evidentiary Support

Extraprostatic extension (EPE) became accepted terminology at a 1996 consensus conference, and replaces earlier ambiguous terms such capsular penetration, perforation, or invasion.[36] In radical prostatectomy specimens EPE is an independent prognostic indicator of increased risk of recurrence post radical prostatectomy and is important in assignment of the AJCC/UICC T category.[37,38] There is limited data specifically on the significance of EPE in needle core biopsies given that it is relatively uncommonly identified; however, it may be occasionally be seen and should be reported when present since it indicates that the tumour is at least pT3a in the TNM system.[30] In needle cores it is defined as tumour admixed with adipocytes, usually at the end of a biopsy core.

It is recommended that the site of any EPE present is recorded since this information is useful for correlation with magnetic resonance imaging (MRI) results and may assist the urologist or radiation oncologist with the technical aspects of treatment planning.

Back

Note 8 - Intraductal carcinoma of prostate (Recommended)

Reason/Evidentiary Support

Intraductal carcinoma of the prostate (IDC-P) is an uncommon finding in needle biopsies cores, hence its absence does not need to be explicitly stated. However, if IDC-P is present it should be recorded and the following comments apply.

IDC-P is usually associated with invasive prostate cancer, however, occasionally isolated IDC-P is found without invasive carcinoma; this latter situation is rare and beyond the scope of this dataset.

IDC-P has been well characterised at the histological and molecular levels over the past decade and its clinical significance is now also better understood.[39] The diagnosis of IDC-P is based on morphology and the key criteria include: 1) large calibre glands that are more than twice the diameter of normal non-neoplastic peripheral glands; 2) preserved (at least focally) basal cells identified on H&E staining (or with basal cell markers, such as p63, keratin 34βE12 and keratin 5/6, however, the use of immunohistochemistry to identify basal cells is optional, rather than mandatory, for the diagnosis of IDC-P); 3) significant nuclear atypia including enlargement and anisonucleosis; and 4) comedonecrosis, which is often but not always present.[40,41] It is important to distinguish IDC-P from high grade prostatic intraepithelial neoplasia (HGPIN): compared to IDC-P, HGPIN has less architectural and cytological atypia, and cribriform HGPIN is rare.

IDC-P is strongly associated with high volume, high grade invasive prostate carcinoma and metastatic disease, hence the presence of IDC-P in a biopsy, even if invasive carcinoma cannot be identified, mandates immediate repeat biopsy or definitive therapy (depending on the clinical situation).[42-45] In a cohort treated with radiation +/- androgen deprivation therapy, the presence of IDC-P in the needle biopsy was an independent predictor of early biochemical recurrence and metastasis.[46]

There was a strong consensus (82%) at the recent ISUP consensus meeting (Chicago 2014) that IDC-P should not be assigned an ISUP or Gleason grade.[47]

⬆ **Back**

Note 9 - Coexistent pathology (Recommended)

Reason/Evidentiary Support

In some cases clinical management decisions may be aided by knowledge of coexisting pathology, such as high grade HGPIN, glandular atypia suspicious for malignancy (atypical small acinar proliferation), granulomatous prostatitis etc.

If there is carcinoma present, the presence of HGPIN is generally not significant, except perhaps occasionally in the situation where the carcinoma is of very limited extent. Even if no cancer is identified in the specimen, the significance of finding HGPIN in needle core biopsies has been controversial with some studies finding an increased risk for detection of prostatic adenocarcinoma in subsequent biopsies, while others did not.[48,49] Recent studies, including one analysing data from a large Canadian cohort, found that this risk was related to the extent of HGPIN, i.e. the number of involved sites; only patients with multifocal HGPIN had a significantly increased risk of prostate cancer.[50-52] Low grade prostatic intraepithelial neoplasia (PIN) should not be reported.

Likewise, if there is carcinoma present in a specimen, the presence of glandular atypia suspicious for malignancy (atypical small acinar proliferation) is generally not significant, except perhaps occasionally in the situation where the carcinoma is of very limited extent. In specimens where there is no cancer identified but glandular atypia is present, the risk of carcinoma being present in subsequent biopsies is approximately 50%.[53-56]

Active prostatitis and granulomatous prostatitis may cause a rise in serum prostate-specific antigen (PSA), although inflammatory lesions may coexist with carcinoma and it is important not to assume that their presence always accounts for an unexplained increase in a patient's PSA.

⬆ **Back**

References

1 World Health Organization (2016). *World Health Organization (WHO) Classification of tumours. Pathology and genetics of the urinary system and male genital organs*. Humphrey PA, Moch H, Reuter VE, Ulbright TM, editors. IARC Press, Lyon, France.

2 Christensen WN, Steinberg G, Walsh PC and Epstein JI (1991). Prostatic duct adenocarcinoma. Findings at radical prostatectomy. *Cancer* 67:2118-2124.

3 Rubenstein JH, Katin MJ, Mangano MM, Dauphin J, Salenius SA, Dosoretz DE and Blitzer PH (1997). Small cell anaplastic carcinoma of the prostate: seven new cases, review of the literature, and discussion of a therapeutic strategy. *Am J Clin Oncol* 20:376-380.

4 Dundore PA, Cheville JC, Nascimento AG, Farrow GM and Bostwick DG (1995). Carcinosarcoma of the prostate. Report of 21 cases. *Cancer* 76:1035-1042.

5 Osunkoya AO and Epstein JI (2007). Primary mucin-producing urothelial-type adenocarcinoma of prostate: report of 15 cases. *Am J Surg Pathol* 31:1323-1329.

6 Curtis MW, Evans AJ and Srigley J (2005). Mucin-producing urothelial-type adenocarcinoma of prostate: report of two cases of a rare and diagnostically challenging entity. *Mod Pathol* 18:585-590.

7 Epstein JI, Allsbrook WCJ, Amin MB and Egevad LL (2005). The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol* 29(9):1228–1242.

8 Morash C, Tey R, Agbassi C, Klotz L, McGowan T, Srigley J and Evans A (2015). Active surveillance for the management of localized prostate cancer: Guideline recommendations. *Can Urol Assoc J* 9(5-6):171-178.

9 Egevad L, Delahunt B, Samaratunga H and Srigley JR (2016). Utility of Reporting the Percentage of High-grade Prostate Cancer. *Eur Urol* 69(4):599-600.

10 Kattan MW, Stapleton AM, Wheeler TM and Scardino PT (1997). Evaluation of a nomogram used to predict the pathologic stage of clinically localized prostate carcinoma. *Cancer* 79(3):528-537.

11 Harnden P, Shelley MD, Naylor B, Coles B and Mason MD (2008). Does the extent of carcinoma in prostatic biopsies predict prostate-specific antigen recurrence? A systematic review. *Eur Urol* 54(4):728-739.

12 Kattan MW, Eastham JA, Stapleton AM, Wheeler TM and Scardino PT (1998). A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst* 90(10):766–771.

13 Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ, Jr., Dotan ZA, Fearn PA and Kattan MW (2006). Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Natl Cancer Inst* 98(10):715-717.

14 D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D and Chen MH (2003). Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol* 21(11):2163-2172.

15 Srigley JR, Delahunt B, Egevad L, Samaratunga H and Evans AJ (2014). Optimising pre-analytical factors affecting quality of prostate biopsies: the case for site specific labelling and single core submission. *Pathology* 46(7):579-580.

16 Srigley JR, Humphrey PA, Amin MB, Chang SS, Egevad L, Epstein JI, Grignon DJ, McKiernan JM, Montironi R, Renshaw AA, Reuter VE and Wheeler TM (2009). Protocol for the examination of specimens from patients with carcinoma of the prostate gland. *Arch Pathol Lab Med* 133(10):1568-1576.

17 Amin MB, Lin DW, Gore JL, Srigley JR, Samaratunga H, Egevad L, Rubin M, Nacey J, Carter HB, Klotz L, Sandler H, Zietman AL, Holden S, Montironi R, Humphrey PA, Evans AJ, Epstein JI, Delahunt B, McKenney JK, Berney D, Wheeler TM, Chinnaiyan AM, True L, Knudsen B and Hammond ME (2014). The critical role of the pathologist in determining eligibility for active surveillance as a management option in patients with prostate cancer: consensus statement with recommendations supported by the College of American Pathologists, International Society of Urological Pathology, Association of Directors of Anatomic and Surgical Pathology, the New Zealand Society of Pathologists, and the Prostate Cancer Foundation. *Arch Pathol Lab Med* 138(10):1387-1405.

18 Vargas SO, Jiroutek M and Welch WR et al (1999). Perineural invasion in prostate needle biopsy specimens: correlation with extraprostatic extension at resection. *Am J Clin Pathol* 111:223-228.

19 de la Taille A, Rubin MA, Bagiella E, Olsson CA, Buttyan R, Burchardt T, Knight C, O'Toole KM and Katz AE (1999). Can perineural invasion on prostate needle biopsy predict prostate specific antigen recurrence after radical prostatectomy? *J Urol* 162(1):103-106.

20 Sebo TJ, Cheville JC, Riehle DL, Lohse CM, Pankratz VS, Myers RP, Blute ML and Zincke H (2002). Perineural invasion and MIB-1 positivity in addition to Gleason score are significant preoperative predictors of progression after radical retropubic prostatectomy for prostate cancer. *Am J Surg Pathol* 26(4):431-439.

21 Loeb S, Epstein JI, Humphreys EB and Walsh PC (2010). Does perineural invasion on prostate biopsy predict adverse prostatectomy outcomes? *BJU Int* 105:1510-1513.

22 Quinn DI, Henshall SM and Brenner PC et al (2003). Prognostic significance of preoperative factors in localised prostate cancer treated with radical prostatectomy; importance of percentage of biopsies that contain tumor and the presence of biopsy perineural invasion. *Cancer* 97:1884-1893.

23 Yu HH, Song DY and Tsai YY et al (2007). Perineural invasion affects biochemical recurrence-free survival in patients with prostate cancer treated with definitive external beam radiotherapy. *Urology* 70:111-116.

24 Egan AJ and Bostwick DG (1997). Prediction of extraprostatic extension of prostate cancer based on needle biopsy findings: perineural invasion lacks significance on multivariate analysis. *Am J Surg Pathol* 21:1496-1500.

25 O'Malley KJ, Pound CR, Walsh PC, Epstein JI and Partin AW (2002). Influence of biopsy perineural on long-term biochemical disease-free survival after radical prostatectomy. *Urology* 59:85-90.

26 Bismar TA, Lewis JS, Vollmer RT and Humphrey PA (2003). Multiple measures of carcinoma extent versus perineural invasion in prediction of pathologic stage in a screening population. *Am J Surg Pathol* 27:432-440.

27 Elharram M, Margel D, Finelli A, Trachtenberg J, Evans A, van der Kwast TH, Sweet JM and Fleshner N (2012). Perineural invasion on prostate biopsy does not predict adverse pathological outcome. *Can J Urol* 19(6):6567-6572.

28 Harnden P, Shelley MD and Clements H et al (2007). The prognostic significance of perineural invasion in prostate cancer biopsies. A systemic review. *Cancer* 109:13-24.

29 Berney DM, Wheeler TM, Grignon DJ, Epstein JI, Griffiths DF, Humphrey PA, van der Kwast T, Montironi R, Delahunt B, Egevad L, Srigley JR and ISUP Prostate Cancer Group (2011). International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. Working group 4: seminal vesicles and lymph nodes. *Mod Pathol* 24:39-47.

30 Amin M.B., Edge, S., Greene, F.L., Byrd, D.R., Brookland, R.K., Washington, M.K., Gershenwald, J.E., Compton, C.C., Hess, K.R., Sullivan, D.C., Jessup, J.M., Brierley, J.D., Gaspar, L.E., Schilsky, R.L., Balch, C.M., Winchester, D.P., Asare, E.A., Madera, M., Gress, D.M., Meyer, L.R. (Eds.) (2017). *AJCC Cancer Staging Manual 8th ed.* Springer, New York.

31 Brierley JD, Gospodarowicz MK, Whittekind C, editors. *UICC TNM Classification of Malignant Tumours, 8th Edition*. Wiley-Blackwell.

32 Herman CM, Wilcox GE, Kattan MW, Scardino PT and Wheeler TM (2000). Lymphovascular invasion as a predictor of disease progression in prostate cancer. *Am J Surg Pathol* 24(6):859–863.

33 Cheng L, Jones TD, Lin H, Eble JN, Zeng G, Carr MD and Koch MO (2005). Lymphovascular invasion is an independent prognostic factor in prostatic adenocarcinoma. *J Urol* 174(6):2181–2185.

34 Yee DS, Shariat SF, Lowrance WT, Maschino AC, Savage CJ, Cronin AM, Scardino PT and Eastham JA (2011). Prognostic significance of lymphovascular invasion in radical prostatectomy specimens. *BJU Int* 108:502-507.

35 May M, Kaufmann O, Hammermann F and Siegsmund M (2007). Prognostic impact of lymphovascular invasion in radical prostatectomy specimens. *BJU Int* 99:539-544.

36 Sakr WA, Wheeler TM, Blute M, Bodo M, Calle-Rodrigue R, Henson DE, Mostofi FK, Seiffert J, Wojno K and Zincke H (1996). Staging and reporting of prostate cancer-sampling of the radical prostatectomy specimen. *Cancer* 78(2):366–368.

37 Wheeler TM, Dillioglugil O, Kattan MW, Arakawa A, Soh S, Suyama K, Ohori M and Scardino PT (1998). Clinical and pathological significance of the level and extent of capsular invasion in clinical stage T1-2 prostate cancer. *Hum Pathol* 29(8):856–862.

38 Epstein JI, Partin AW, Sauvageot J and Walsh PC (1996). Prediction of progression following radical prostatectomy. A multivariate analysis of 721 men with long-term follow-up. *Am J Surg Pathol* 20(3):286–292.

39 Zhou M (2013). Intraductal carcinoma of the prostate: the whole story. *Pathology.* 45(6):533-539.

40 Cohen RJ, Wheeler TM, Bonkhoff H and Rubin MA (2007). A proposal on the identification, histologic reporting, and implications of intraductal prostatic carcinoma. *Arch Pathol Lab Med* 131(7):1103-1109.

41 Guo CC and Epstein JI (2006). Intraductal carcinoma of the prostate on needle biopsy: Histologic features and clinical significance. *Mod Pathol.* 19(12):1528-1535.

42 Kovi J, Jackson MA and Heshmat MY (1985). Ductal spread in prostatic carcinoma. *Cancer* 56(7):1566-1573.

43 McNeal JE and Yemoto CE (1996). Spread of adenocarcinoma within prostatic ducts and acini. Morphologic and clinical correlations. *Am J Surg Pathol* 20(7):802-814.

44 Robinson BD and Epstein JI (2010). Intraductal carcinoma of the prostate without invasive carcinoma on needle biopsy: emphasis on radical prostatectomy findings. *J Urol* 184(4):1328-1333.

45 Zhao T, Liao B, Yao J, Liu J, Huang R, Shen P, Peng Z, Gui H, Chen X, Zhang P, Zhu Y, Li X, Wei Q, Zhou Q, Zeng H and Chen N (2015). Is there any prognostic impact of intraductal carcinoma of prostate in initial diagnosed aggressively metastatic prostate cancer? *Prostate* 75(3):225-232.

46 Van der Kwast T, Al Daoud N, Collette L, Sykes J, Thoms J, Milosevic M, Bristow RG, Van Tienhoven G, Warde P, Mirimanoff RO and Bolla M (2012). Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. *Eur J Cancer* 48(9):1318-1325.

47 Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR and Humphrey PA (2015). 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. *Am J Surg Pathol* 40(2):244-52.

48 Epstein JI and Herawi M (2006). Prostatic needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. *J Urol* 175:820-834.

49 Schlesinger C, Bostwick DG and Iczkowski KA (2005). High-grade intraepithelial neoplasia and atypical small acinar proliferation: predictive value for cancer in current practice. *Am J Surg Pathol* 29:1201-1207.

50 Merrimen JL, Jones G, Walker D, Leung CS, Kapusta LR and Srigley JR (2009). Multifocal high grade prostatic intraepithelial neoplasia is a significant risk factor for prostatic carcinoma. *J. Urology* 182:485-490.

51 Merrimen JL, Jones G and Srigley JR (2010). Is high grade prostatic intraepithelial neoplasia still a risk factor for adenocarcinoma in the era of extended biopsy sampling? *Pathology* 42:325-329.

52 Akhavan A, Keith JD and al Be (2007). The proportion of cores with high-grade prostatic intreaepithelial neoplasia on extended pattern needle biopsy is significantly associated with prostatic cancer on site directed repeat biopsy. *BJU Int* 99:765-769.

53 Iczkowski KA, MacLennan GT and Bostwick DG (1997). Atypical small acinar proliferation suspicious for malignancy in prostate needle biopsies: clinical significance in 33 cases. *Am J Surg Pathol* 21(12):1489-1495.

54 Iczkowski KA, Chen HM, Yang XJ and Beach RA (2002). Prostate cancer diagnosed after initial biopsy with atypical small acinar proliferation suspicious for malignancy is similar to cancer found on initial biopsy. *Urology* 60(5):851-854.

55 Mancuso PA, Chabert C, Chin P, Kovac P, Skyring T, Watt WH and Napaki S (2007). Prostate cancer detection in men with an initial diagnosis of atypical small acinar proliferation. *BJU Int* 99(1):49-52.

56 Cheville JC, Reznicek MJ and Bostwick DG (1997). The focus of "atypical glands, suspicious for malignancy" in prostatic needle biopsy specimens: incidence, histologic features, and clinical follow-up of cases diagnosed in a community practice. *Am J Clin Pathol* 108(6):633-640.