PATHOLOGICA 2020;112:17-24;
DOI: 10.32074/1591-951X-5-20

Review

Intraductal carcinoma of the prostate

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Summary
Intraductal carcinoma of the prostate (IDC-P) is a diagnostic entity characterized by architecturally or cytologically malignant-appearing prostatic glandular epithelium confined to prostatic ducts. Despite its apparent *in situ* nature, this lesion is associated with aggressive prostatic adenocarcinoma and is a predictor for poor prognosis when identified on biopsy or radical prostatectomy. This review discusses diagnosis, clinical features, histogenesis, and management of IDC-P, as well as current research and controversies surrounding this entity.

Key words: intraductal carcinoma, prognosis, prostate carcinoma, aggressive prostate cancer

Introduction

Despite its apparent *in situ* nature, intraductal carcinoma of the prostate (IDC-P) is associated with aggressive behavior and poor outcome. While this may appear counterintuitive, current theories on histogenesis of IDC-P suggest that many of these lesions represent adenocarcinoma with retrograde invasion into the prostatic ducts [1]. Thus, most IDC-P are not biologically or pathologically distinct from conventional prostatic adenocarcinoma but rather a morphologic manifestation of the aggressive nature of the underlying cancer. An overview of the clinical and pathological features of IDC-P will be provided herein with an emphasis on current research and controversies regarding this entity.

Epidemiology and diagnostic criteria

First described in an autopsy study in 1938 [2], IDC-P became more widely studied in the mid-1980's with the increasing use of immunohistochemistry [3,4]. Diagnostic criteria for IDC-P were first proposed by Guo and Epstein in 2006 (Tab. I, Fig. 1A-1D) and subsequently endorsed by the World Health Organization (WHO) tumor classification, which recognized IDC-P as a distinct entity in 2016 [5,6]. The WHO defines IDC-P as an "intra-acinar and/or intraductal neoplastic epithelial proliferation that has some features of high grade prostatic intraepithelial neoplasia (HG-PIN) but exhibits much greater architectural and/or cytological atypia, typically associated with high grade or high stage prostate carcinoma" [6]. The prevalence of IDC-P is largely dependent on the patient cohort, ranging from 2-3% in low-risk or overall patient cohorts [7,8] to 67% in metastatic/recurrent disease [8-10] for biopsy specimens, and 13-17% in radical prostatectomy (RP) specimens [11,12].

Received and accepted: January 7, 2020

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Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Szentirmai E, Giannico GA. Intraductal carcinoma of the prostate. Pathologica 2020;112:17-24. https://doi.org/10.32074/1591-951X-5-20

Table I. Diagnostic criteria for IDC-P (left panel) and AIP (right panel). Adapted from Guo & Epstein 2006 [5] and Shah et al. 2017 [15].

Intraductal carcinoma of the prostate	Atypical intraductal proliferation
1. Malignant epithelial cells filling large acini and prostatic ducts a. Solid or dense cribriform pattern with cellular density > 50% of luminal space b. Loose cribriform or micropapillary pattern with either i. Marked nuclear atypia with nuclei at least 6x larger than adjacent benign nuclei or ii. Nonfocal comedonecrosis 2. Preservation of basal cells	1. Malignant epithelial cells filling large acini and prostatic ducts a. Solid or dense cribriform pattern incompletely spanning the lumen with cellular density < 50% of luminal space b. Loose cribriform or micropapillary pattern with both i. Insufficient nuclear pleomorphism to meet diagnostic criteria for IDC-P ii. Absence of necrosis 2. Preservation of basal cells

Lesions that do not meet morphologic criteria for IDC-P but appear more complex than HGPIN either architecturally or cytologically have been termed "atypical intraductal proliferations" (AIP) [13-15] (Tab. I, Fig. 1E-F).

Clinical features and reporting recommendations

IDC-P is independently associated with adverse clinical and pathological features on both biopsy and RP. Specifically, RP studies have shown that patients with IDC-P have higher pathologic T stage [10,16-18], higher Gleason score [10,16-20], increased tumor volume [3,4,10,16-19], and increased likelihood of extraprostatic extension [5,10,16,20], seminal vesicle invasion [10,19], and lymph node metastases [10,20]. These patients also have an increased risk of biochemical recurrence [21,22] and metastasis [22] and worse progression-free, cancer-specific, and overall survival [10,20].

Patients with IDC-P detected on biopsy have higher Gleason score and likelihood of seminal vesicle invasion on RP [7] as well as worse progression-free, cancer-specific, and overall survival [23-25]. While the finding of IDC-P on biopsy is highly specific for detection of IDC-P on RP, the sensitivity is relatively low (56.5% overall and 34.1% for active surveillance cohorts), making a positive finding more prognostically valuable than a negative one [26].

In the setting of metastatic disease, patients with IDC-P show worse cancer-specific and overall survival [23,27,28] and increased likelihood of development of castration-resistant prostate cancer (CRPC) [28]. In metastatic CRPC, IDC-P is a predictor of decreased cancer-specific and overall survival [29-31] as well as early relapse following neoadjuvant chemotherapy [32], relapse following androgen deprivation therapy [33] and radiation therapy [9]. IDC-P is also highly prevalent after androgen deprivation therapy or chemotherapy (60%) [8].

There is some heterogeneity in outcomes reported with different patterns of IDC-P. Solid and dense cribriform patterns are prognostically more unfavorable than loose cribriform or micropapillary patterns in localized [19] and metastatic disease [27].

While conventional IDC-P represents retrograde spread of invasive high grade carcinoma and is associated with aggressive features at RP, studies have suggested that isolated IDC-P or IDC-P with low grade adenocarcinoma may represent a precursor, *de novo* lesion associated with better clinical outcome [34-36]. The former category is termed "regular type" IDC-P, as opposed to "precursor-like" IDC-P, which is considered a precursor to invasive adenocarcinoma [34]. These two entities are currently pathologically indistinguishable. Isolated IDC-P, i.e., IDC-P without concurrent invasive carcinoma is found in 0.1-0.3% of biopsies [7,35].

Lesions diagnosed as AIP have clinical features more similar to IDC-P than to HGPIN. Patients with AIP and IDC-P on needle biopsy do not have a significantly different incidence of associated invasive carcinoma, although invasive carcinoma associated with IDC-P has higher Gleason score and higher percentage of needle core involvement on biopsy [15]. Patients with a diagnosis of AIP without associated prostate cancer on needle core biopsy have a 50% likelihood of a subsequent diagnosis of invasive carcinoma or IDC-P [13]. On RP, patients with invasive carcinoma and AIP or IDC-P have similar clinicopathologic characteristics, including no significant difference in Gleason score, tumor stage, seminal vesicle invasion, and surgical margins [11,12]. Patients with AIP carry an intermediate risk of biochemical recurrence between those with IDC-P and HGPIN [12].

There is significant controversy as to whether IDC-P should be included in the Grade Group system. Based on recent studies showing that IDC-P/cribriform architecture is a poor prognostic factor independent of Grade Group [37,38], some groups advocate its incorporation into the Grade Group system [37,39]. However,

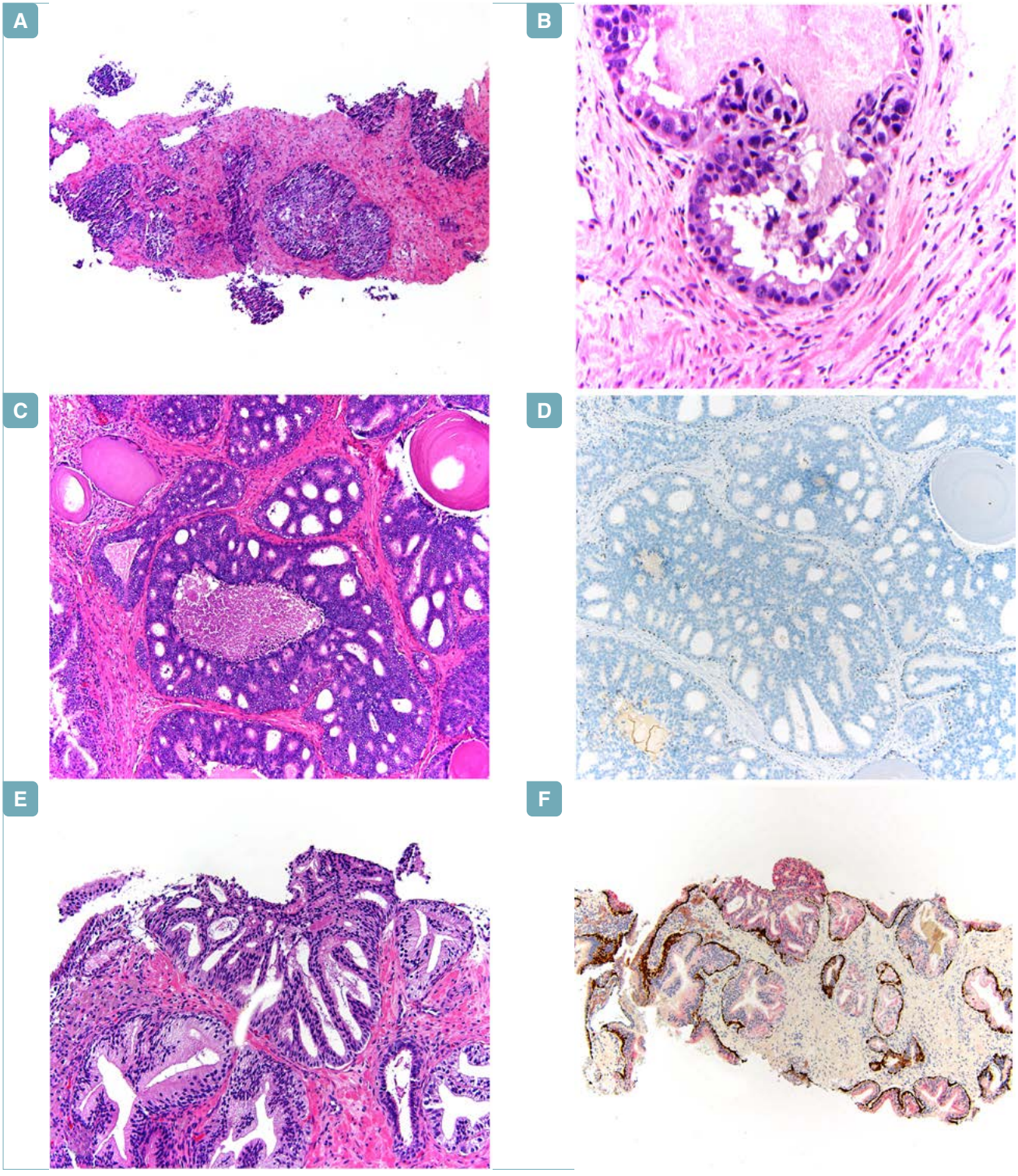

Figure 1. Intraductal carcinoma of the prostate (IDC-P) and atypical intraductal proliferation (AIP): (A) Solid pattern of IDC-P (Original magnification ×40); (B) Nuclei 6x larger than those of adjacent benign cells (Original magnification ×200); (C) Dense cribriform pattern with comedonecrosis (Original magnification ×100); (D) Preserved basal cell staining by immunohistochemistry for p63 (Original magnification ×100). (E) Loose cribriform pattern with lack of pleomorphism and comedonecrosis in AIP (Original magnification ×100); (F) Preserved basal cell staining and AMACR positivity in AIP (Triple stain with p63, HMWCK and AMACR) (Original magnification ×40).

in view of the limited evidence on the association of IDC-P with low-grade invasive carcinoma, as well as the overlapping morphology of precursor-like and regular type IDC-P, some authors argue against incorporating IDC-P into the Grade Group system [40]. Furthermore, precursor-like and isolated IDC-P have a different expression pattern of PTEN and ERG from the concurrent low-grade cancer, suggesting that isolated IDC-P is unrelated to the associated low-grade invasive prostate cancer [41]. Currently, the European Association of Urology (EAU) guidelines do not support assigning a grade to IDC-P and recommend reporting IDC-P separately from Grade Group [42].

Differential diagnosis

IDC-P shares morphologic features with several entities. HGPIN is a precursor for prostatic adenocarcinoma and its diagnosis on biopsy (if unifocal, i.e. limited to one core) does not increase the risk of carcinoma detection on repeat biopsy [43,44]. Similarly to IDC-P, HGPIN consists of cytologically malignant cells confined to ducts or acini; however, HGPIN will not demonstrate the same degree of cellular density, architectural and cytologic atypia, or necrosis that are typical of IDC-P (Tab. I, Fig. 1A-1D). In practice, especially in the setting of limited tissue, this distinction is not straightforward, as some IDC-P can have a low-grade appearance [45]. Both IDC-P and HGPIN have preservation of basal cells and both express AMACR by immunohistochemistry. Immunohistochemical ERG expression or PTEN loss may be helpful to support a diagnosis of IDC-P in this context, as these features are not typical of HGPIN [13,46-48] (Fig. 2).

The distinction between IDC-P and invasive acinar adenocarcinoma (cribriform Gleason pattern 4 or solid Gleason pattern 5) can be challenging on H&E sections, but it can be easily resolved by immunohistochemistry with the former displaying basal cell staining and the latter having complete loss of basal cells. Given that IDC-P is confined by ducts, these will have smoother contours, well circumscribed borders and follow a more organized branching architecture [5]. The presence of comedonecrosis strongly suggests a diagnosis of IDC-P [49], while perineural invasion or extraprostatic extension favor invasive carcinoma [50,51]. As both entities represent high grade malignancy, clinical management is similar [52,53].

Despite similarities in nomenclature, IDC-P and ductal adenocarcinoma have distinct morphologies. Ductal adenocarcinoma is characterized by tall pseudostratified columnar cells commonly forming true papillae with fibrovascular cores and sometimes displaying cribriform architecture. IDC-P has cuboidal (acinar) cells, can display micropapillary architecture without fibrovascular cores, and has a greater degree of cytologic atypia. Notably, ductal adenocarcinoma can occasionally involve the ducts and demonstrate persistence of basal cell markers. In these cases, a diagnosis of “intraductal carcinoma with ductal features” is rendered. Ductal adenocarcinoma is graded as Gleason pattern 4 [6].

Urothelial carcinoma involving prostatic ducts can sometimes be challenging to distinguish from the solid pattern of IDC-P on H&E. Extreme pleomorphism, high mitotic activity or apoptosis, and dense eosinophilic cytoplasm are morphologic features that favor urothelial carcinoma, while any glandular differentiation favors IDC-P. Fortunately, these entities are easily distinguishable by immunohistochemical markers as IDC-P will stain with prostatic markers, e.g. PSA, PSAP, p501s, and NKX3.1, while urothelial carcinoma will stain with HMWCK, p63, and GATA3. This distinction is important for management, as urothelial carcinoma involving prostatic ducts will be managed with radical cystoprostatectomy [43,52].

Molecular features and histogenesis

The most common early molecular aberration in prostatic adenocarcinoma is the fusion between the androgen regulated serine protease *TMPRSS2* and members of the ETS transcription factor family, most commonly *ERG,* driving overexpression of the *ERG* oncogene [54-56]. This rearrangement is mutually exclusive with other early driver mutations such as those involving *SPOP*. The prognostic significance of the *TMPRSS2-ERG* rearrangement is unclear [57-61]. Additional second line genetic alterations, all associated with more aggressive disease, include *PTEN*, *TP53, RB1, MYC,* and *BRCA2* [54,62,63]. Of these, *PTEN* loss has been the most studied and has been shown to be significantly associated with high Gleason grade, advanced tumor stage, and decreased time to metastasis [64,65]. Large scale genomic alterations, including copy number alterations, deletions, gains, and fusions comprise the majority of genetic alterations in prostate cancer.

IDC-P predominantly shows *TMPRSS2-ERG* fusion as an early driver mutation and has numerous second line genetic alterations associated with aggressive and metastatic disease (Fig. 2). Of note, HGPIN harbors the *TMPRSS2-ERG* fusion as well as *PTEN* loss much less frequently [10,66-69], while prevalence of these alterations in AIP is more similar to that seen

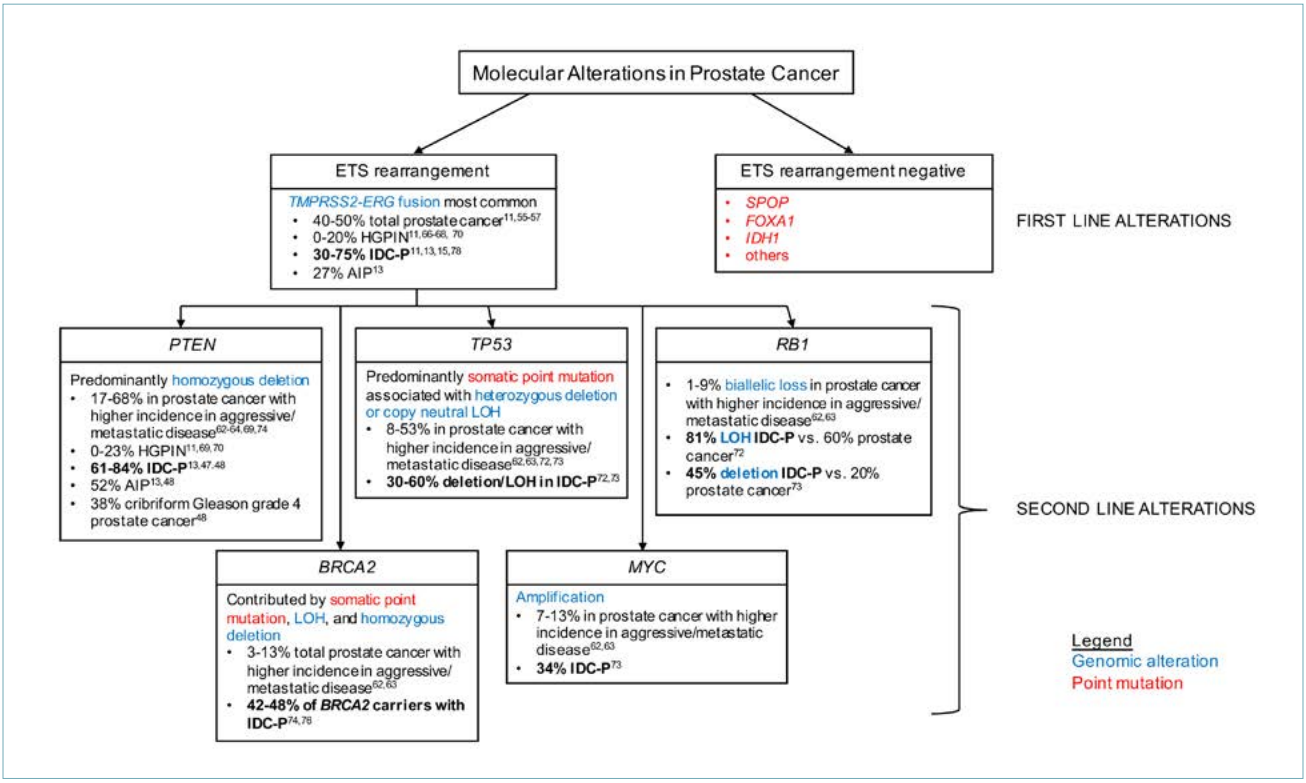

Figure 2. Molecular alterations in intraductal carcinoma (highlighted in bold) and invasive carcinoma of the prostate.

in IDC-P [48,70]. Loss of heterozygosity (LOH), chromosomal imbalances, and percent genomic alteration have been found to be significantly higher in IDC-P compared with invasive prostate carcinoma and much higher than those seen in HGPIN [22,71-73].

Patients with germline mutations in genes associated with DNA repair (most commonly *BRCA2*, *ATM*, *CHEK2*, *BRCA1*) and *BRCA2* specifically have been found to have a higher incidence of IDC-P [74-76], prompting recommendations for germline genetic testing in patients with this diagnosis even in the absence of family history [77].

Molecular findings also provide evidence for the histogenesis of IDC-P. Intraductal carcinoma and adjacent acinar adenocarcinoma share the same *TMPRSS2-ERG* genomic breakpoints, supporting the idea of a common clonal origin [1,78]. Additionally, invasive carcinoma adjacent to IDC-P with PTEN loss also shows similar PTEN abnormality, suggesting that IDC-P represents retrograde colonization of ducts by a subclone of an invasive carcinoma. The aggressiveness of this subclone is highlighted by the presence of similar copy number alteration patterns in IDC-P and metastasis [79].

Molecular findings also provide evidence for the distinction between regular type and precursor-like IDC-P. A subset of isolated IDC-P showed molecular alterations in the MAPK/PI3K pathway that are distinct from those of regular type IDC-P and conventional acinar adenocarcinoma [41]. This heterogeneity in IDC-P makes its categorization and clinical ramifications difficult and requires further research.

Management

There is no consensus on the management of IDC-P. Given the association of IDC-P with high grade and high volume invasive carcinoma on RP, the majority of authors recommend definitive therapy or suggest immediate re-biopsy when IDC-P is diagnosed. This is true even in the absence of invasive carcinoma [5,18,35,52] or with low grade, Gleason 3 + 3 = 6 carcinoma [36,52]. Because AIP on biopsy is associated with an increased risk of invasive carcinoma or IDC-P [13,48], this diagnosis warrants immediate re-biopsy [15]. Reporting IDC-P on radical prostatectomy is useful for prognostic purposes and for recommendation of germline testing; otherwise, clinical management is decided on a case by case basis [52,77].

Conclusions

IDC-P is associated with aggressive prostate cancer, early biochemical recurrence, and decreased survival. Diagnosis and early reporting are paramount for patient management due to significant therapeutic and prognostic implications. Further studies are needed to address current unresolved issues and fully understand the biological nature of this entity.

References

1 Haffner MC, C Weier, MM Xu, et al. Molecular evidence that invasive adenocarcinoma can mimic prostatic intraepithelial neoplasia (PIN) and intraductal carcinoma through retrograde glandular colonization. J Pathol 2016;238:31-41. https://doi.org/10.1002/path.4628

2 Gaynor EP, Zur Frage des Prostatakrebses. Virchows Arch 1938;301:602-52. https://doi.org/10.1007/BF02595173

3 Kovi J, MA Jackson, and MY Heshmat, Ductal spread in prostatic carcinoma. Cancer 1985;56:1566-73. https://doi.org/10.1002/1097-0142(19851001)56:7<1566::aid-cncr2820560717>3.0.co;2-y

4 McNeal JE, JH Reese, EA Redwine, et al. Cribriform adenocarcinoma of the prostate. Cancer 1986;58:1714-9. https://doi.org/10.1002/1097-0142(19861015)58:8<1714::aid-cncr2820580823>3.0.co;2-m

5 Guo CC and JI Epstein, Intraductal carcinoma of the prostate on needle biopsy: Histologic features and clinical significance. Mod Pathol 2006;19:1528-35. https://doi.org/10.1038/modpathol.3800702

6 Moch H HP, Ulbright TM, Reuter V., WHO Classification of Tumours of the Urinary System and Male Genital Organs, ed. IAfRo Cancer. Lyon, France

7 Watts K, J Li, C Magi-Galluzzi, et al. Incidence and clinicopathological characteristics of intraductal carcinoma detected in prostate biopsies: a prospective cohort study. Histopathology 2013;63:574-9. https://doi.org/10.1111/his.12198

8 Porter LH, MG Lawrence, D Ilic, et al. Systematic Review Links the Prevalence of Intraductal Carcinoma of the Prostate to Prostate Cancer Risk Categories. Eur Urol 2017;72:492-95. https://doi.org/10.1016/j.eururo.2017.03.013

9 Van der Kwast T, N Al Daoud, L Collette, et al. Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. Eur J Cancer 2012;48:1318-25. https://doi.org/10.1016/j.ejca.2012.02.003

10 Kimura K, T Tsuzuki, M Kato, et al. Prognostic value of intraductal carcinoma of the prostate in radical prostatectomy specimens. Prostate 2014;74:680-7. https://doi.org/10.1002/pros.22786

11 Han B, K Suleman, L Wang, et al. ETS gene aberrations in atypical cribriform lesions of the prostate: Implications for the distinction between intraductal carcinoma of the prostate and cribriform high-grade prostatic intraepithelial neoplasia. Am J Surg Pathol 2010;34:478-85. https://doi.org/10.1097/PAS.0b013e3181d6827b

12 Miyai K, MK Divatia, SS Shen, et al. Clinicopathological analysis of intraductal proliferative lesions of prostate: intraductal carcinoma of prostate, high-grade prostatic intraepithelial neoplasia, and atypical cribriform lesion. Hum Pathol 2014;45:1572-81. https://doi.org/10.1016/j.humpath.2014.03.011

13 Morais CL, JS Han, J Gordetsky, et al. Utility of PTEN and ERG immunostaining for distinguishing high-grade PIN from intraductal carcinoma of the prostate on needle biopsy. Am J Surg Pathol 2015;39:169-78. https://doi.org/10.1097/PAS.0000000000000348

14 Shah RB, C Magi-Galluzzi, B Han, et al. Atypical cribriform lesions of the prostate: relationship to prostatic carcinoma and implication for diagnosis in prostate biopsies. Am J Surg Pathol 2010;34:470-7. https://doi.org/10.1097/PAS.0b013e3181cfc44b

15 Shah RB, J Yoon, G Liu, et al. Atypical intraductal proliferation and intraductal carcinoma of the prostate on core needle biopsy: a comparative clinicopathological and molecular study with a proposal to expand the morphological spectrum of intraductal carcinoma. Histopathology 2017;71:693-702. https://doi.org/10.1111/his.13273

16 Rubin MA, A de La Taille, E Bagiella, et al. Cribriform carcinoma of the prostate and cribriform prostatic intraepithelial neoplasia: incidence and clinical implications. Am J Surg Pathol 1998;22:840-8. https://doi.org/10.1097/00000478-199807000-00006

17 Cohen RJ, WC Chan, SG Edgar, et al. Prediction of pathological stage and clinical outcome in prostate cancer: an improved pre-operative model incorporating biopsy-determined intraductal carcinoma. Br J Urol 1998;81:413-8. https://doi.org/10.1046/j.1464-410x.1998.00530.x

18 Cohen RJ, TM Wheeler, H Bonkhoff, et al. A proposal on the identification, histologic reporting, and implications of intraductal prostatic carcinoma. Arch Pathol Lab Med 2007;131:1103-9.

19 Wilcox G, S Soh, S Chakraborty, et al. Patterns of high-grade prostatic intraepithelial neoplasia associated with clinically aggressive prostate cancer. Hum Pathol 1998;29:1119-23. https://doi.org/10.1016/s0046-8177(98)90423-3

20 Dinerman BF, F Khani, R Golan, et al. Population-based study of the incidence and survival for intraductal carcinoma of the prostate. Urol Oncol 2017;35:673 e9-73 e14. https://doi.org/10.1016/j.urolonc.2017.08.015

21 O'Brien BA, RJ Cohen, TM Wheeler, et al. A post-radical-prostatectomy nomogram incorporating new pathological variables and interaction terms for improved prognosis. BJU Int 2011;107:389-95. https://doi.org/10.1111/j.1464-410X.2010.09539.x

22 Chua MLK, W Lo, M Pintilie, et al. A Prostate Cancer "Nimbosus": Genomic Instability and SChLAP1 Dysregulation Underpin Aggression of Intraductal and Cribriform Subpathologies. Eur Urol 2017;72:665-74. https://doi.org/10.1016/j.eururo.2017.04.034

23 Kato M, K Kimura, A Hirakawa, et al. Prognostic parameter for high risk prostate cancer patients at initial presentation. Prostate 2018;78:11-16. https://doi.org/10.1002/pros.23438

24 Kweldam CF, IP Kummerlin, D Nieboer, et al. Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. Mod Pathol 2016;29:630-6. https://doi.org/10.1038/modpathol.2016.49

25 Saeter T, L Vlatkovic, G Waaler, et al. Intraductal Carcinoma of the Prostate on Diagnostic Needle Biopsy Predicts Prostate Cancer Mortality: A Population-Based Study. Prostate 2017;77:859-65. https://doi.org/10.1002/pros.23326

26 Ericson KJ, S Wu, SD Lundy, et al. Diagnostic Accuracy of Prostate Biopsy for Detecting Cribriform Gleason Pattern 4 Carcinoma and Intraductal Carcinoma in Paired Radical Prostatectomy Specimens: Implications for Active Surveillance. J Urol 2019:101097JU0000000000000526. https://doi.org/10.1097/JU.0000000000000526

27 Zhao J, J Liu, G Sun, et al. The Prognostic Value of the Proportion and Architectural Patterns of Intraductal Carcinoma of the Prostate in Patients with De Novo Metastatic Prostate Cancer. J Urol 2019;201:759-68. https://doi.org/10.1016/j.juro.2018.10.016

[28] Zhao T, B Liao, J Yao, et al. Is there any prognostic impact of intraductal carcinoma of prostate in initial diagnosed aggressively metastatic prostate cancer? Prostate 2015;75:225-32. https://doi.org/10.1002/pros.22906

[29] Yamamoto A, M Kato, H Matsui, et al. Efficacy of docetaxel in castration-resistant prostate cancer patients with intraductal carcinoma of the prostate. Int J Clin Oncol 2018;23:584-90. https://doi.org/10.1007/s10147-017-1235-6

[30] Chen Z, N Chen, P Shen, et al. The presence and clinical implication of intraductal carcinoma of prostate in metastatic castration resistant prostate cancer. Prostate 2015;75:1247-54. https://doi.org/10.1002/pros.23005

[31] Zhao J, P Shen, G Sun, et al. The prognostic implication of intraductal carcinoma of the prostate in metastatic castration-resistant prostate cancer and its potential predictive value in those treated with docetaxel or abiraterone as first-line therapy. Oncotarget 2017;8:55374-83. https://doi.org/10.18632/oncotarget.19520

[32] O'Brien C, LD True, CS Higano, et al. Histologic changes associated with neoadjuvant chemotherapy are predictive of nodal metastases in patients with high-risk prostate cancer. Am J Clin Pathol 2010;133:654-61. https://doi.org/10.1309/AJCP8EL5FTZSOBIH

[33] Efstathiou E, NA Abrahams, RF Tibbs, et al. Morphologic characterization of preoperatively treated prostate cancer: toward a post-therapy histologic classification. Eur Urol 2010;57:1030-8. https://doi.org/10.1016/j.eururo.2009.10.020

[34] Miyai K, MK Divatia, SS Shen, et al. Heterogeneous clinicopathological features of intraductal carcinoma of the prostate: a comparison between "precursor-like" and "regular type" lesions. Int J Clin Exp Pathol 2014;7:2518-26.

[35] Robinson BD and JI Epstein, Intraductal carcinoma of the prostate without invasive carcinoma on needle biopsy: emphasis on radical prostatectomy findings. J Urol 2010;184:1328-33. https://doi.org/10.1016/j.juro.2010.06.017

[36] Khani F and JI Epstein, Prostate Biopsy Specimens With Gleason 3+3=6 and Intraductal Carcinoma: Radical Prostatectomy Findings and Clinical Outcomes. Am J Surg Pathol 2015;39:1383-9. https://doi.org/10.1097/PAS.0000000000000465

[37] Kato M, A Hirakawa, YM Kobayashi, et al. The influence of the presence of intraductal carcinoma of the prostate on the grade group system's prognostic performance. Prostate 2019;79:1065-70. https://doi.org/10.1002/pros.23818

[38] Kweldam CF, GJ van Leenders, and T van der Kwast, Grading of prostate cancer: a work in progress. Histopathology 2019;74:146-60. https://doi.org/10.1111/his.13767

[39] van Leenders G, CF Kweldam, E Hollemans, et al. Improved Prostate Cancer Biopsy Grading by Incorporation of Invasive Cribriform and Intraductal Carcinoma in the 2014 Grade Groups. Eur Urol 2019. https://doi.org/10.1016/j.eururo.2019.07.051

[40] Epstein JI, Is There Enough Support for a New Prostate Grading System Factoring in Intraductal Carcinoma and Cribriform Cancer? Eur Urol 2019. https://doi.org/10.1016/j.eururo.2019.08.022

[41] Khani F, SE Wobker, JL Hicks, et al. Intraductal carcinoma of the prostate in the absence of high-grade invasive carcinoma represents a molecularly distinct type of in situ carcinoma enriched with oncogenic driver mutations. J Pathol 2019;249:79-89. https://doi.org/10.1002/path.5283

[42] Mottet N BJ, Briers E, Bolla M, Bourke L, Cornford P, De Santis M, Henry A, Joniau S, Lam T, Mason MD, Van den Poel H, Van den Kwast TH, Rouvière O, Wiegel T;members of the EAU – ESTRO – ESUR –SIOG Prostate Cancer Guidelines Panel. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. [cited 2019 15 Nov];Available from: https://uroweb.org/guideline/prostate-cancer/

[43] Wobker SE and JI Epstein, Differential Diagnosis of Intraductal Lesions of the Prostate. Am J Surg Pathol 2016;40:e67-82. https://doi.org/10.1097/PAS.0000000000000609

[44] Epstein JI NG. Biopsy interpretation of the prostate. Fifth edition, ed. WKHA (ESP), 2014.

[45] Zhou M, Intraductal carcinoma of the prostate: the whole story. Pathology 2013;45:533-9. https://doi.org/10.1097/PAT.0b013e3283653322

[46] Shah RB and M Zhou, Atypical cribriform lesions of the prostate: clinical significance, differential diagnosis and current concept of intraductal carcinoma of the prostate. Adv Anat Pathol 2012;19:270-8. https://doi.org/10.1097/PAP.0b013e31825c6c0e

[47] Lotan TL, B Gumuskaya, H Rahimi, et al. Cytoplasmic PTEN protein loss distinguishes intraductal carcinoma of the prostate from high-grade prostatic intraepithelial neoplasia. Mod Pathol 2013;26:587-603. https://doi.org/10.1038/modpathol.2012.201

[48] Shah RB, KT Shore, J Yoon, et al. PTEN loss in prostatic adenocarcinoma correlates with specific adverse histologic features (intraductal carcinoma, cribriform Gleason pattern 4 and stromogenic carcinoma). Prostate 2019;79:1267-73. https://doi.org/10.1002/pros.23831

[49] Fine SW, HA Al-Ahmadie, YB Chen, et al. Comedonecrosis Revisited: Strong Association With Intraductal Carcinoma of the Prostate. Am J Surg Pathol 2018;42:1036-41. https://doi.org/10.1097/PAS.0000000000001104

[50] Kronz JD, AA Shaikh, and JI Epstein, Atypical cribriform lesions on prostate biopsy. Am J Surg Pathol 2001;25:147-55. https://doi.org/10.1097/00000478-200102000-00002

[51] Epstein JI, Mimickers of prostatic intraepithelial neoplasia. Int J Surg Pathol 2010;18:142S-48S. https://doi.org/10.1177/1066896910370616

[52] Magers M, LP Kunju, and A Wu, Intraductal Carcinoma of the Prostate: Morphologic Features, Differential Diagnoses, Significance, and Reporting Practices. Arch Pathol Lab Med 2015;139:1234-41. https://doi.org/10.5858/arpa.2015-0206-RA

[53] Divatia MK and JY Ro, Intraductal Carcinoma of the Prostate Gland: Recent Advances. Yonsei Med J 2016;57:1054-62. https://doi.org/10.3349/ymj.2016.57.5.1054

[54] Arora K and CE Barbieri, Molecular Subtypes of Prostate Cancer. Curr Oncol Rep 2018;20:58. https://doi.org/10.1007/s11912-018-0707-9

[55] Tomlins SA, DR Rhodes, S Perner, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 2005;310:644-8. https://doi.org/10.1126/science.1117679

[56] Tomlins SA, A Bjartell, AM Chinnaiyan, et al. ETS gene fusions in prostate cancer: from discovery to daily clinical practice. Eur Urol 2009;56:275-86. https://doi.org/10.1016/j.eururo.2009.04.036

[57] Wang J, Y Cai, C Ren, et al. Expression of variant TMPRSS2/ERG fusion messenger RNAs is associated with aggressive prostate cancer. Cancer Res 2006;66:8347-51. https://doi.org/10.1158/0008-5472.CAN-06-1966

[58] Rajput AB, MA Miller, A De Luca, et al. Frequency of the TMPRSS2:ERG gene fusion is increased in moderate to poorly differentiated prostate cancers. J Clin Pathol 2007;60:1238-43. https://doi.org/10.1136/jcp.2006.043810

[59] Nam RK, L Sugar, Z Wang, et al. Expression of TMPRSS2:ERG gene fusion in prostate cancer cells is an important prognostic factor for cancer progression. Cancer Biol Ther 2007;6:40-5. https://doi.org/10.4161/cbt.6.1.3489

[60] Gopalan A, MA Leversha, JM Satagopan, et al. TMPRSS2-ERG gene fusion is not associated with outcome in patients treated by prostatectomy. Cancer Res 2009;69:1400-6. https://doi.org/10.1158/0008-5472.CAN-08-2467

[61] Pettersson A, RE Graff, SR Bauer, et al. The TMPRSS2:ERG rearrangement, ERG expression, and prostate cancer outcomes: a cohort study and meta-analysis. Cancer Epidemiol Biomarkers Prev 2012;21:1497-509. https://doi.org/10.1158/1055-9965.EPI-12-0042

[62] Cancer Genome Atlas Research N, The Molecular Taxonomy of Primary Prostate Cancer. Cell 2015;163:1011-25. https://doi.org/10.1016/j.cell.2015.10.025

[63] Robinson D, EM Van Allen, YM Wu, et al. Integrative Clinical Genomics of Advanced Prostate Cancer. Cell 2015;162:454. https://doi.org/10.1016/j.cell.2015.06.053

[64] Krohn A, T Diedler, L Burkhardt, et al. Genomic deletion of PTEN is associated with tumor progression and early PSA recurrence in ERG fusion-positive and fusion-negative prostate cancer. Am J Pathol 2012;181:401-12. https://doi.org/10.1016/j.ajpath.2012.04.026

[65] Lotan TL, B Gurel, S Sutcliffe, et al. PTEN protein loss by immunostaining: analytic validation and prognostic indicator for a high risk surgical cohort of prostate cancer patients. Clin Cancer Res 2011;17:6563-73. https://doi.org/10.1158/1078-0432.CCR-11-1244

[66] Cerveira N, FR Ribeiro, A Peixoto, et al. TMPRSS2-ERG gene fusion causing ERG overexpression precedes chromosome copy number changes in prostate carcinomas and paired HG-PIN lesions. Neoplasia 2006;8:826-32. https://doi.org/10.1593/neo.06427

[67] Mosquera JM, S Perner, EM Genega, et al. Characterization of TMPRSS2-ERG fusion high-grade prostatic intraepithelial neoplasia and potential clinical implications. Clin Cancer Res 2008;14:3380-5. https://doi.org/10.1158/1078-0432.CCR-07-5194

[68] Perner S, JM Mosquera, F Demichelis, et al. TMPRSS2-ERG fusion prostate cancer: an early molecular event associated with invasion. Am J Surg Pathol 2007;31:882-8. https://doi.org/10.1097/01.pas.0000213424.38503.aa

[69] Yoshimoto M, JC Cutz, PA Nuin, et al. Interphase FISH analysis of PTEN in histologic sections shows genomic deletions in 68% of primary prostate cancer and 23% of high-grade prostatic intraepithelial neoplasias. Cancer Genet Cytogenet 2006;169:128-37. https://doi.org/10.1016/j.cancergencyto.2006.04.003

[70] Morais CL, LB Guedes, J Hicks, et al. ERG and PTEN status of isolated high-grade PIN occurring in cystoprostatectomy specimens without invasive prostatic adenocarcinoma. Hum Pathol 2016;55:117-25. https://doi.org/10.1016/j.humpath.2016.04.017

[71] Dawkins HJ, LN Sellner, GR Turbett, et al. Distinction between intraductal carcinoma of the prostate (IDC-P), high-grade dysplasia (PIN), and invasive prostatic adenocarcinoma, using molecular markers of cancer progression. Prostate 2000;44:265-70. https://doi.org/10.1002/1097-0045(20000901)44:4<265::aid-pros1>3.0.co;2-i

[72] Bettendorf O, H Schmidt, A Staebler, et al. Chromosomal imbalances, loss of heterozygosity, and immunohistochemical expression of TP53, RB1, and PTEN in intraductal cancer, intraepithelial neoplasia, and invasive adenocarcinoma of the prostate. Genes Chromosomes Cancer 2008;47:565-72. https://doi.org/10.1002/gcc.20560

[73] Bottcher R, CF Kweldam, J Livingstone, et al. Cribriform and intraductal prostate cancer are associated with increased genomic instability and distinct genomic alterations. BMC Cancer 2018;18:8. https://doi.org/10.1186/s12885-017-3976-z

[74] Risbridger GP, RA Taylor, D Clouston, et al. Patient-derived xenografts reveal that intraductal carcinoma of the prostate is a prominent pathology in BRCA2 mutation carriers with prostate cancer and correlates with poor prognosis. Eur Urol 2015;67:496-503. https://doi.org/10.1016/j.eururo.2014.08.007

[75] Taylor RA, M Fraser, J Livingstone, et al. Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. Nat Commun 2017;8:13671. https://doi.org/10.1038/ncomms13671

[76] Isaacsson Velho P, JL Silberstein, MC Markowski, et al. Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate 2018;78:401-07. https://doi.org/10.1002/pros.23484

[77] Network NCC. Prostate cancer (version 4.2019). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) August 19,2019 [cited 2019 12/31];Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

[78] Schneider TM and AO Osunkoya, ERG expression in intraductal carcinoma of the prostate: comparison with adjacent invasive prostatic adenocarcinoma. Mod Pathol 2014;27:1174-8. https://doi.org/10.1038/modpathol.2013.248

[79] Lindberg J, A Kristiansen, P Wiklund, et al. Tracking the origin of metastatic prostate cancer. Eur Urol 2015;67:819-22. https://doi.org/10.1016/j.eururo.2014.09.006