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Review – Prostate Cancer

Impact of Epithelial Histological Types, Subtypes, and Growth Patterns on Oncological Outcomes for Patients with Nonmetastatic Prostate Cancer Treated with Curative Intent: A Systematic Review

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Abstract

Context: The optimal management for men with prostate cancer (PCa) with unconventional histology (UH) is unknown. The outcome for these cancers might be worse than for conventional PCa and so different approaches may be needed.
Objective: To compare oncological outcomes for conventional and UH PCa in men with localized disease treated with curative intent.
Evidence acquisition: A systematic review adhering to the Referred Reporting Items for Systematic Reviews and Meta-Analyses was prospectively registered on PROSPERO (CRD42022296013) was performed in July 2021.
Evidence synthesis: We screened 3651 manuscripts and identified 46 eligible studies (reporting on 1 871 814 men with conventional PCa and 6929 men with 10 different PCa UHs). Extraprostatic extension and lymph node metastases, but not positive margin rates, were more common with UH PCa than with conventional tumors. PCa cases with cribriform pattern, intraductal carcinoma, or ductal adenocarcinoma had higher rates of biochemical recurrence and metastases after radical prostatectomy than for conventional PCa cases. Lower cancer-specific survival rates were observed for mixed cribriform/intraductal and cribriform PCa. By contrast, pathological findings and oncological outcomes for mucinous and prostatic intraepithelial neoplasia (PIN)-like PCa were similar to those for conventional PCa. Limitations of this review include low-quality studies, a risk of reporting bias, and a scarcity of studies that included radiotherapy.
Conclusions: Intraductal, cribriform, and ductal UHs may have worse oncological outcomes than for conventional and mucinous or PIN-like PCa. Alternative treatment approaches need to be evaluated in men with these cancers.
Patient summary: We reviewed the literature to explore whether prostate cancers with unconventional growth patterns behave differently to conventional prostate cancers. We found that some unconventional growth patterns have worse outcomes, so we need to investigate if they need different treatments. Urologists should be aware of these growth patterns and their clinical impact.

1. Introduction

According to the latest World Health Organization (WHO) classification of tumors, prostate cancer (PCa) can be subclassified according to histological types, subtypes, and growth patterns. While approximately 95% of patients are diagnosed with conventional acinar adenocarcinoma (namely, conventional PCa), 5% have an unconventional histology (UH) [1]. As PCa is the most common solid cancer among men, this UH percentage would translate into a relevant absolute number of patients and an epidemiological burden worldwide [2].

Preliminary evidence showed certain UHs have greater or lower disease aggressiveness [3,4] in comparison to conventional PCa. Hence, new entities were introduced in the WHO 2016 classification [4] and further confirmed in 2022 [1]. According to the International Society of Urological Pathology (ISUP) 2019 consensus conference [5] and the Genitourinary Pathology Society white paper [6], cribriform growth pattern and intraductal PCa must now be routinely reported. Comprehensive knowledge of UHs, their biological behavior, and their potential impact on outcomes may be of value in the clinical decision-making process. Thus, there is a need to confirm the association of UHs with different outcomes in comparison to conventional PCa. Moreover, whether certain UHs may benefit from a specific PCa treatment modality also requires investigation.

The generalizability of reviews that assessed the prognostic implications of specific UHs, including neuroendocrine [7,8] and intraductal [3,9] disease is limited by the use of nonstandardized methodology [7] and the inclusion of patients with metastatic disease [7]. The European Association of Urology (EAU) Young Academic Urologists Prostate Cancer Working Party (YAU PCa-WP) and the EAU PCa Guidelines Panel systematically reviewed the literature to assess oncological outcomes for patients with localized PCa and UH treated with curative intent (radical prostatectomy [RP] or radiation therapy [RT]).

2. Evidence synthesis

2.1. Aims

Our primary objective was to describe and compare oncological outcomes for (1) patients with pure/mixed UH in comparison to patients with conventional acinar adenocarcinoma of the prostate without these features (comparator) and (2) different treatment modalities within the context of a specific pure/mixed UH.

The secondary objective was to assess whether UH presence is associated with higher incidence of extraprostatic extension (EPE), positive surgical margins (PSMs), lymph node invasion (LNI), and/or seminal vesicle invasion in com-

parison to conventional PCa at final pathology for patients treated with RP.

2.2. Protocol and measures

An a priori protocol was registered on PROSPERO (CRD42022296013) after review and approval by the EAU-YAU PCa-WP and the EAU PCa Guidelines Panel and the EAU Methods Panel. Using a Patient, Intervention, Comparison, Outcome (PICO) approach, cN0M0 PCa cases with mixed/pure UH were investigated. Two comparisons were considered for the search and review: (1) UH versus conventional PCa; and (2) different curative treatment modalities (eg, RP vs RT) for each UH.

The primary outcomes were cancer-specific mortality and prostate-specific antigen (PSA) relapse. Additional outcomes included overall mortality after adjuvant/salvage therapies stratified by type of treatment; metastasis-free survival (MFS), defined as the percentage of patients free from metastatic disease, overall survival (OS), and pTNM stage at RP.

The risk of bias (RoB) and study quality were assessed according to the EAU recommendations for systematic reviews and meta-analysis [10]. The Cochrane RoB assessment tool was used for randomized controlled trials (RCTs) and the quality appraisal tool for case series, using a modified Delphi technique for retrospective studies [11] as previously described [12]. Complications were reported according to the EAU Guidelines on Complications Reporting [13]. The data extraction form is provided in the Supplementary material.

2.3. Study inclusion criteria

We included single-arm cohort studies and/or comparative prospective and retrospective studies reporting on ≥20 patients with epithelial or neuroendocrine UH at prostate biopsy or RP. Patients had to be treated with RP and/or RT (any type) with curative intent. Neoadjuvant or adjuvant treatments were allowed. We focused exclusively on men with nonmetastatic PCa on conventional imaging. In the case of multiple reports for the same cohort, the most complete data aggregated over the longest follow-up were considered. Similarly, in the case of multiple reports for the same cohort or overlapping patients, studies were included only if they added relevant prognostic information in comparison to the other reports for the same cohort.

We excluded studies that did not separately report outcomes for UH, those focusing only on salvage treatments without providing data on the primary treatment/first PCa diagnosis, and investigations reporting on non-epithelial or non-neuroendocrine UH or with inappropriate UH pathological definitions.

Registry-based studies were included to verify whether population-based outcomes mirror those of single- and multi-institutional series. Results from registry-based evidence are presented in a separate paragraph because of (1) multiple articles using the same data set with a consequent potential risk of data duplication and (2) no possibility to review the pathology criteria used to define the UHs.

2.4. Search strategy

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1).

The literature search was carried out using the Medline and Embase databases and the Cochrane register on July 27, 2021 for English language articles published after 2000. The search strategy is provided in the Supplementary material. Two authors (F.Z. and C.K.) screened all records and performed data extraction. Discrepancies were solved by a third author (G.M.). At the end of the process, an independent review of the data quality of the records retrieved was performed by two authors (G.M. and P.R.). Finally, a genitourinary pathologist with PCa expertise (G.J.L.H.v.L.) reviewed the pathological definitions for the UHs and the methodology in all the full texts included to confirm the appropriateness of the pathological inclusion criteria [1,5]. Although all the studies were published before the 5th edition of the WHO [1], the results are reported according to this classification. A summary of the pathological criteria and an overview of the UHs included in the present work is provided in Figure 2. The term "unconventional histology" (UH) was adopted after collegial discussion to facilitate generalization of our findings, even though it is not used in the WHO 5th edition, which comprises categories, types, subtypes and growth patterns [1].

3. Evidence synthesis

3.1. Study characteristics

Overall, 46 retrospective studies reporting outcomes for 1 878 743 men were identified, of whom 6929 had one of ten UHs. These included 40 retrospective single-center or multicenter series (16 545 men, 3538 with UHs) and six registry-based studies (n = 1 862 198 men, 3391 with UHs). The UHs included cribriform, intraductal, ductal, mucinous, and PIN-like PCa; in addition, registry-based studies included adenosquamous, sarcomatoid, small cell, neuroendocrine overall, and signet-ring–like PCa. Overall, the quality of the studies was low (Table 1 [14–59] and Supplementary Table 1). Patients were recruited between 1985 and 2019, although the majority of studies (n = 26) included men diagnosed after 2000. Twenty-one cohorts were from multiple centers; 33 studies conducted a complete pathological review (1–5 pathologists involved, and blinded to clinical features in 15 studies). Thirty-one studies used RP as the reference, eight used biopsy alone, four used RP and/or biopsy, and three used biopsy and/or transurethral resection.

3.2. Retrospective series: UHs vs conventional PCa

3.2.1. Baseline and pathological characteristics

Seven centers were involved in two or more studies on UHs, with a potential for duplication of patient data (Supplementary Table 2). Thirteen series evaluated a cribriform growth pattern and intraductal type together as a single entity because their distinction often requires the use of immunohistochemistry. No cohort studies on neuroendocrine carci-

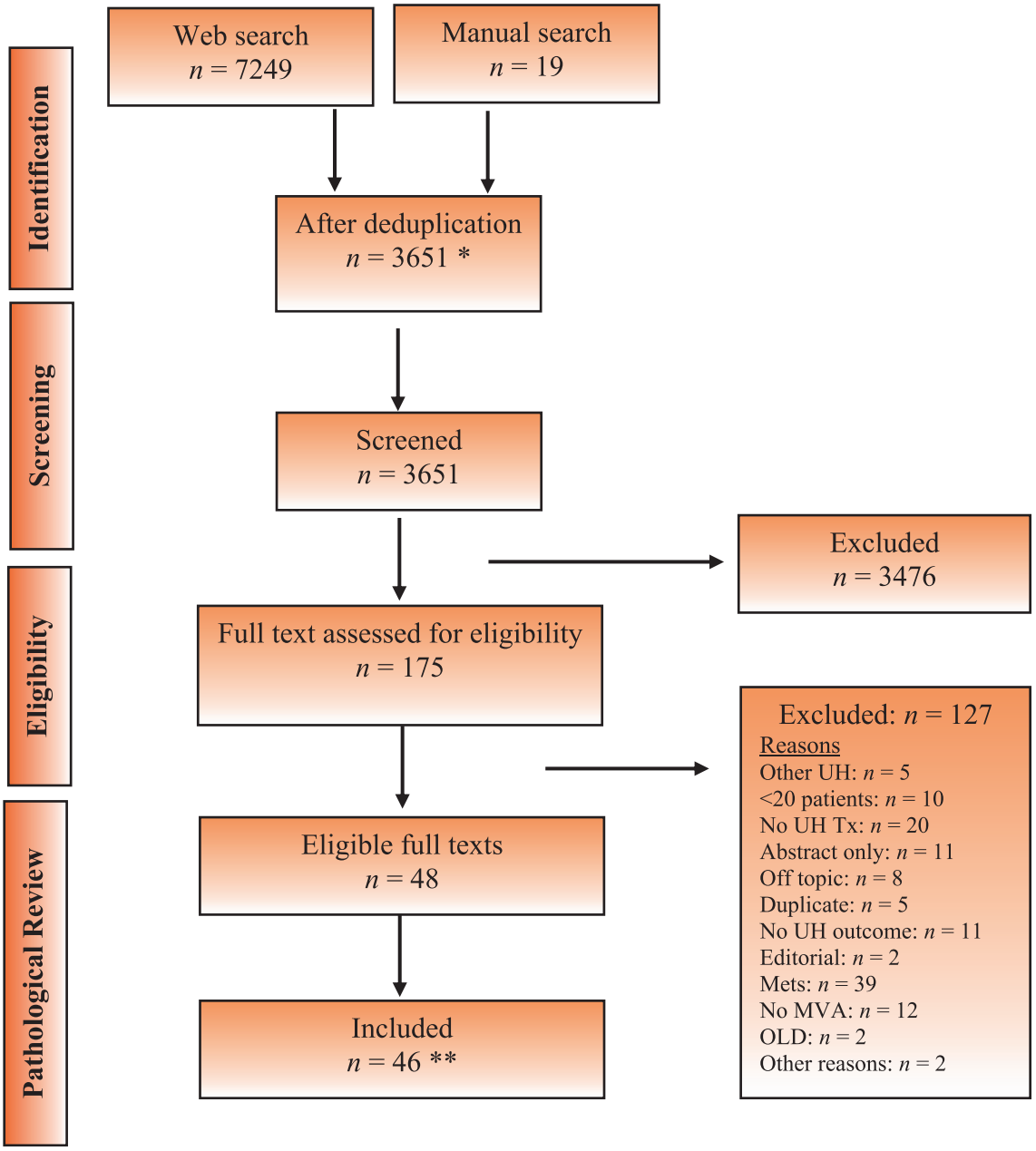

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. *Full texts that were reviews were also excluded. Other UH = other unconventional histology not detailed; No UH Tx = treatment details for unconventional histology were not separately available or treatment was performed without curative intent; No HV outcome = outcomes for unconventional histology not separately reported; Mets = patients with metastatic disease at diagnosis were included and outcomes are not reported separately for men with localized disease; No MVA = no multivariable analysis performed for prognostic factors or no treatment included in multivariable analysis; OLD = first publication on a previous series without any additional information compared to the latest publication; Other reasons = no study criteria reported (*n* = 1) and study not performed on human subjects (*n* = 1). **Two articles excluded after pathological review were by Tu et al. [63] and Patil et al. [64].

noma identified. Table 2 lists the baseline PCa characteristics in the studies. The median patient age was <70 yr in all studies. Median PSA ranged from 5.2 ng/ml [14] to 33.6 ng/ml [15], and was >10 ng/ml in seven studies (*n* = 4 ductal [16–19], *n* = 2 intraductal [15,20], *n* = 1 cribriform/intraductal [21]). Some studies assessed the impact of UH in a prespecified ISUP grade group (GG) and/or Gleason score (GS) group, including intraductal/cribriform in GG 2 (*n* = 4 [22–25]), GG 4 [24], and GG 5 [21] PCa, and cribriform pattern alone in GS 7 PCa [26]. The majority of patients with UH had concomitant GS 7, including cribriform/intraductal (69%, *n* = 564 had GS 7), ductal (64%, *n* = 187), intraductal (56%, *n* = 126), cribriform (100%, *n* = 120), and mucinous (91%, *n* = 37) UHs. Overall, only four cases (0.1%) of cribriform/intraductal PCa and only 16 (6%) of intraductal PCa alone were associated with GG 1 PCa. Conversely, a significant proportion of mucinous and PIN-like UH cases were diagnosed among men with GG 1 PCa (mucinous 13%; PIN-like 66%).

Overall, final pathology at RP revealed EPE in more than half of the specimens for intraductal/cribriform (61%, *n* = 384), ductal (80%, *n* = 459), and cribriform alone (83%,

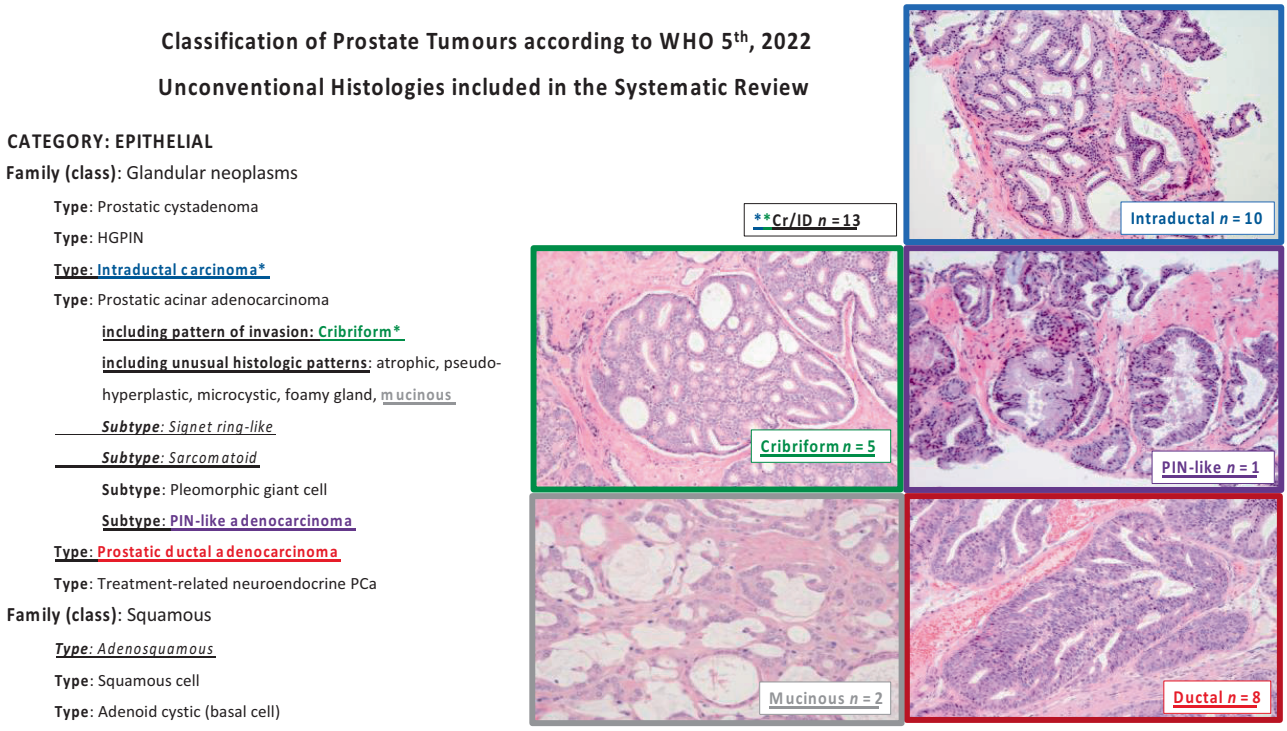

Fig. 2 – Prostate tumors identified in articles included in the systematic review according to the World Health Organization (WHO) 2022 classification. In the 2022 WHO edition, neuroendocrine neoplasms (not included in this figure, although they were searched for and were assessed in registry-based studies) are included as a separate chapter, similar to tumors of the bladder and tumors of the prostate. The reason for this is that the morphology, immunohistochemistry, behavior, and treatment of these specific tumors is the same in diverse organ systems such as the urinary bladder and prostate. The neuroendocrine family is described at the end of the caption. A small shift in terminology in the 2022 WHO edition is that the term "variant" in reference to a specific type of tumor has been wholly superseded by "subtype" in an effort to more clearly differentiate this meaning from that of "variant" in reference to a genetic alteration. Bold and underscored text denotes types or subtypes or patterns for which single-center or multicenter retrospective studies ± registry-based studies were identified; the number of studies indicates the number of retrospective cohorts with the unconventional histology included in the present systematic review. **Cr/ID = the number of studies that included cribriform pattern (a pattern of invasion of acinar type) and/or intraductal type evaluated together, as immunohistochemistry is needed for differential diagnosis confirmation. Italic and underscored text denote types and/or subtypes and/or patterns for which only registry-based studies were identified; images of these unconventional histologies are not included in the figure. HGPIN = high-grade prostatic intraepithelial neoplasia. Intraductal carcinoma is a cribriform proliferation of atypical epithelial cells within and expanding a pre-existent acinar structure. Immunohistochemical staining demonstrates the presence of basal cells, compatible with a pre-existent gland. Invasive cribriform carcinoma is a contiguous proliferation of atypical epithelial cells with a round nucleus without intervening stroma showing round, punched-out intercellular lumina. Basal cells are absent (immunohistochemistry not shown). PIN-like adenocarcinoma is visible as organized glands with short papillary infoldings covered by atypical epithelial cells reminiscent of HGPIN. In contrast to HGPIN, the glandular proliferation entirely lacks basal cells (immunohistochemistry not shown); Ductal adenocarcinoma is composed of papillary structures and/or complex and cribriform glands lined by tall columnar pseudostratified cells. Mucinous adenocarcinoma is a primary acinar adenocarcinoma with ≥25% of the tumor composed of glands with extraluminal mucin. The neuroendocrine chapter recognizes (i) neuroendocrine tumors: well-differentiated neuroendocrine tumor (8240/3 and 8249/3); (ii) neuroendocrine carcinomas: (a) small cell neuroendocrine carcinoma (8041/3); (b) large cell neuroendocrine carcinoma (8013/3); and (c) mixed neuroendocrine neoplasms; and (iii) paraganglioma.

n=69) UHs, while EPE was described in 44% (n = 31) of cases with intraductal carcinoma.

Studies comparing pathological stage between UH and conventional PCa are summarized in Supplementary Table 3. Higher rates of EPE at final pathology in comparison to conventional PCa were reported for cribriform/intraductal (6 studies [21,22,24,25,27,36], ductal (4 studies [16,19,28,29]), intraductal (1 study [30]), and cribriform PCa (1 study [31]). This was confirmed on multivariable analysis for cribriform/intraductal (1 study [25]), ductal (2 studies [17,32]), and intraductal PCa (1 study [15]). Two matched-pair studies assessing ductal and intraductal subtypes did not find significant differences in the proportion of patients with EPE after matching (p = 0.6 [28] and p = 0.5 [15]).

Overall, rates of PSM at RP ranged from 13% for mucinous PCa to >40% for ductal (43%, n = 238), intraductal (58%, n = 21), and cribriform (43%, n = 35) UHs. In studies comparing PSMs in UH versus conventional PCa, the PSM rate was significantly higher in a minority of the series (1/4 cribriform/intraductal studies [22], 1/2 ductal studies [19], and 1/4 intraductal studies [15]) and the association was not confirmed in multivariable analyses [15,19].

Information on lymphadenectomy (8 studies [16,21,24,26,33–36]) and LNI (7 studies [16,21,24,33–36]) was poorly reported (Table 2). Rates of pN+ status ranged from 2.5% for mucinous PCa to 21% for cribriform/intraductal UH in GG 4 disease. Some studies highlighted significantly higher LNI rates in UH than in conventional PCa on univariable analysis (3/4 cribriform/intraductal studies [22,24,36], 3/4 ductal studies [16,19,29], and 1/2 cribriform studies [33]). Multivariable analysis for LNI was performed in only two studies, revealing significantly higher LNI risk for cribriform/intraductal UH [36] but not for ductal PCa

Table 1 – Baseline features, methodology, and exclusion criteria for the studies included in the review

General study features			Pathology				Study exclusion criteria			
Study	Accrual	Setting	Pathologists	Blinded	Sample[a]	Bx technique	M+	cN+	nADT	Other
Retrospective series										
Cribriform and intraductal prostate cancer evaluated together										
Hollemans et al. [38]	2000–2017	S	2	Yes	RP	–	NS	NS	Exc	RT, GTx
Hollemans et al. [22]	2000–2017	S	2	Yes	RP	–	NS	NS	Exc	RT, GTx
Hollemans et al. [24]	2000–2017	M	2	Yes	RP	–	NS	NS	Exc	RT, GTx
Hansum et al. [21]	2000–2017	M	2	Yes	RP	–	NS	NS	Exc	RT, GTx
Kweldam et al. [14]	1993–2000	S	3	Yes	Bx	Sextant	Exc	NS	NS	Slides NA
Kweldam et al. [41]	1993–2000	S	3	Yes	Bx	Sextant	Exc	NS	NS	Slides NA
Kweldam et al. [23]	1993–2000	S	3	Yes	Bx	Sextant	Exc	Exc	NS	Slides NA
Tontilla et al. [37]	2014–2016	S	2	Yes	RP	–	Exc	NS	NS	3-T mpMRI before RP
Chua et al. [40]	1987–2012	M	5	No	Bx/RP	NS	Exc	NS	Inc	NS
Masoomian e al [25]	2015–2018	M	–	–	RP	–	NS	NS	NS	NS
Trudel et al. [39][b]	1998–2001	S	2	No	RP	–	NS	NS	NS	ID
Efstathiou et al. [27]	NS	S	2	No	RP	–	NS	NS	Inc	NS
Downes et al. [36]	2005–2018	M	–	–	Bx/RP	NS	NS	NS	NS	ID
Ductal prostate cancer										
Jang et al. [16]	2005–2014	SC	–	–	RP	–	NS	NS	Exc	aTx, ID
Samaratunga et al. [32]	2004	SC	Yes[c]	NS	RP	–	NS	NS	NS	NS
Kim et al. [17]	1999–2013	SC	2	NS	RP	–	NS	Ns	NS	HGPIN-like DC
Jeong et al. [18]	1995–2015	SC	2	Yes	RP	–	NS	NS	Exc	ITM, no FU
Vinceneux et al. [34]	2000 & 2015	MC	4	No	RP	–	Exc	NS	NS	Insufficient DC component, IFs between cribriform and DC
Chow et al. [28]	2007–2019	MC	Yes[c]	No	RP	–	Exc	NS	Exc	–
Harkin et al. [29]	2007–2017	SC	–	–	RP	NS	Exc	Exc	Exc	ID
Tan et al. [19]	2008–2017	SC	Yes[c]	No	RP	–	NS	NS	NS	aTx
Intraductal prostate cancer										
Kato et al. [45]	1991–2005	MC	1	No	Bx, RP	NS	NS	NS	Inc	Slides NA
Kato et al. [46]	1991–2005	MC	1	No	Bx	NS	NS	NS	NS	ID
Kato et al. [43]	2005–2013	MC	1	No	RP	–	Exc	Exc	Exc	ID
Karakoc et al. [59]	2000–2014	SC	2	Yes	RP	–	NS	NS	NS	Adjuvant RT
O'Brien et al. [42]	1998–2007	MC	1	–	RP	–	NS	NS	Exc	aTx before BCR, ID, no index PCa determined
Van der Kwast et al. [44]	1999–2006, 1987–1995	MC	1 or 2[d]	No	Bx/TUR	NS	NS	NS	Exc	NS
Miyai et al. [20]	2006–2012	SC	2	No	RP	–	NS	NS	Exc	aTx
Zhu et al. [15]	2010–2017	SC	2	No	Bx/RP	TP 12-core SBx	NS	NS	NS	-
Trinh et al. [35]	1993–2011	MC	2	Yes	RP	–	Exc	Exc	Exc	Tissue degradation, no slides available, FU uncertainty
Trinh et al. [30]	1993–2015	MC	2	Yes	RP	–	Exc	Exc	Exc	aTx, PSA persistence
Cribriform prostate cancer										
Kweldam et al. [26]	1985–2013	SC	2	Yes	RP	–	NS	NS	Exc	Slides NA
Leo et al. [48]	NS[e]	MC	Yes[c]	No	RP	–	Exc	NS	Exc	aTx, USD, <30 d RP FU, PSA ≥0.2 ng/ml after RP
Keefe et al. [31]	2010–2015	SC	2	Yes	Bx	TR 10-core SBx	NS	NS	Exc	No GS 7 on TRUS, neoadjuvant Tx
Kir et al. [49]	2006–2013	SC	2	Yes	RP	–	NS	NS	Exc	–
Choy et al. [50]	2003–2006	SC	2	No	RP	–	NS	NS	Inc	Salvage RP
Greenland et al. [47]	2015–2018	SC	–	–	RP	–	NS	NS	NS	Expansile cribriform and glomerulation, pattern 5
Mucinous prostate cancer										
Osunkoya et al. [58]	1991–2006	SC	1	–	RP	–	NS	NS	NS	NS
Samaratunga [33]	2009–2014	SC	Yes[c]	No	RP	–	NS	NS	NS	–
PIN-like prostate cancer										
Tavora et al. [51]	1999–2007	SC	Yes[c]	No	RP	NS	NS	NS	NS	–
Registry-based studies										
Bronkema et al. [55]	2004–2015	MC	NS	–	Bx/TUR	NS	Exc[f]	Exc[f]	NS	ID
Packiam et al. [52]	1998–2011	MC	NS	–	Bx	NS	Exc	Exc	NS	FU <5 yr
Bronkema et al. [53]	2004–2015	MC	NS	–	Bx/TUR	NS	Exc	Exc[f]	Inc	No FU, no Tx information

Table 1 (*continued*)

General study features			Pathology				Study exclusion criteria			
Study	Accrual	Setting	Pathologists	Blinded	Sample[a]	Bx technique	M+	cN+	nADT	Other
Dinerman et al. [56]	2004–2013	MC	NS	No	RP	–	NS	Exc	NS	ID
Patel et al. [57]	2004–2013	MC	NS	–	Bx	NS	Exc	Exc	No	Multiple cancers, RP Dx on autopsy, unknown RT status
Weiner et al. [54]	1998–2011	MC	NS	No	Bx	NS	Exc	Exc	–	Palliative RT

aTx = adjuvant therapy; BCR = biochemical recurrence; Bx = biopsy; DC = ductal carcinoma; Dx = diagnosis; Exc = excluded; FU = follow-up; GS = Gleason score; GTx = gene therapy; HGPIN = high-grade prostatic intraepithelial neoplasia; Inc = included; ID = incomplete data; IFs = intermediate features; ITM = insufficient tissue for microarrays; MC = multiple centers; mpMRI = multiparametric magnetic resonance imaging; NA = not available; nADT = neoadjuvant androgen deprivation therapy; NS = not specified; PCa = prostate cancer; PSA = prostate-specific antigen; SC = single center; RP = radical prostatectomy; RT = radiation therapy; SBx = systematic Bx; TP = transperineal; TR = transrectal; TRUS = transrectal ultrasound; TUR = transurethral resection; Tx = therapy; USD = unsuccessful slide digitization.

[a] Pathological specimen used to assess the presence of the unconventional histology. In cases for which pathological review was performed, this corresponded to the specimen reviewed.

[b] Trudel et al. [39] included large cribriform histology.

[c] Pathology review was performed but the number of pathologists reviewing the specimen was not stated.

[d] For the PMH (Princess Margaret Hospital) cohort, cores were reviewed by two pathologists; for the EORTC (European Organization for Treatment and Research of Cancer) cohort, specimens were reviewed by one pathologist.

[e] Median year of surgery 2007.

[f] Data were extracted from a subgroup analysis of men with no extraprostatic disease.

[19]. PSA persistence after RP was reported in just four studies and was observed in 23% of cribriform/intraductal (n = 28) [37], 29% of ductal (n = 23) [19], and 42% of intraductal cases (n = 15) [15,30].

3.2.2. Oncological outcomes

Oncological outcomes in the retrospective series are shown in Table 3. The oncological outcome most frequently reported was BCR (31 studies); nine studies included MFS. On multivariable analysis, cribriform/intraductal UH presence was an independent predictor of BCR (9 studies [14,21–24,27,38–40], metastasis (3 studies [21,24,40]) and cancer-specific death (1 study [41]) in comparison to conventional PCa. Ductal PCa was associated with a higher risk of BCR on multivariable analysis (4 series [16,19,28,29]) and of metastasis and shorter MFS in one matched-pair analysis [28]. Similarly, intraductal PCa alone was significantly correlated with worse BCR (5 studies [15,20,30,42,43]), metastasis [30,44], and OS [45,46] on multivariable analysis. Cribriform pattern alone was an independent predictor of BCR (5 studies [26,47–50]), metastasis (1 study [26]), and cancer-specific death (1 study [26]). No studies described multivariable analysis for mucinous or PIN-like PCa. After 6–38-mo follow-up after RP, 9.4% of men with mucinous PCa had BCR. No significant differences in comparison to conventional PCa were highlighted [33]. Following RP for PIN-like PCa, no case of BCR or metastasis was reported [51].

3.2.3. RP and RT

Five studies included RT as a primary treatment modality (Supplementary Table 4). One study assessed and reported no significant interaction between cribriform/intraductal PCa and treatment modality [41].

3.3. Registry based studies

The six registry-based studies used the National Cancer Database (n = 4) [52–55] or the Surveillance, Epidemiology and End Results (SEER) database (n = 2) [56,57] to assess ductal (n = 4) [52,53,55,57], intraductal [56], small cell [54] and multiple UHs [55]. Baseline features of the studies are listed in Supplementary Table 5 and outcomes are reported in Supplementary Table 6. For ductal PCa, the 5-yr OS rate (75%) was similar to that for GS 8–10 (p = 0.2) but worse than for GS 6–7 PCa (p < 0.001) overall and after adjusting for confounding factors (GS 6–7: hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.34–0.61; GS 8–10: HR 0.92, 95% CI 0.69–1.23) [52]. Similar trends were confirmed for men undergoing RP as curative treatment [52]. No mortality differences between ductal and conventional PCa were found in another study (p = 0.1) [55]. Among different treatment modalities for ductal adenocarcinoma, one study found better OS for surgery in comparison to observation, systemic therapy, or RT (p < 0.001) [53]. Another study reported that men with ductal UH who received RT had a lower risk of overall mortality (p = 0.042) and PCa-specific death (p = 0.006) in comparison to those treated with "local ablation" (LA), which included transurethral resection, laser ablation, cryotherapy, and "tumor excision", but not RP [57]. Similar results were reported for a matched-pair subgroup (10-yr OS 80% RT vs 46% LA; 10-yr CSS 96% RT vs 69% LA; both p < 0.01). There was no information on concomitant ADT use [57]. Among patients treated with RP, intraductal UH was associated with higher pathological stage, LNI, and PSM (p < 0.01), but not with overall mortality (p > 0.5) [56]. The 5-yr OS reported for small cell PCa was 22% overall, and men who received local treatment (RP or RT) had better 5-yr OS than patients who did not (37% vs 3.1%; p < 0.001). This trend was confirmed on adjusted Cox proportional-hazards regression (p < 0.001) [54]. Overall, in comparison to conventional PCa, mucinous and signet ring cell PCa had similar OS (both p > 0.5). Conversely, small cell, adenosquamous, and sarcomatoid subtypes were associated with worse survival (all p < 0.01) [55].

3.4. Discussion

In the face of a paucity of data on the impact of UH on oncological outcomes for patients with nonmetastatic PCa

Table 2 – Baseline characteristics of the patients included in retrospective series

Study	Subgroups	Patients	pN+		pre–RP PSA (ng/ml)		GG on RP or biopsy, *n* (%)										pT stage, *n* (%)							
		(*n*)	*n*	(%)	Median	(IQR)	GG 1		GG 2		GG 3		GG 4		GG 5		pT2		pT3a		pT3b		pT4	
Hollemans [38]	All PCa	835	33	(3.9)	8.2	(5.7–13.0)	207	(25.0)	420	(50.0)	101	(12.0)	50	(6.0)	57	(7.0)	476	(57.0)	263	(32.0)	93	(11.0)	3	(0.4)
	Cr/ID	**417**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hollemans [22]	All (GG 1–2)	627					–	–	–	–	–	–	–	–	–	–	419	(66.8)	173	(27.6)	35	(5.6)	0	(0.0)
	GG 1	207	0	(0.0)	6.3	(4.0–9.2)	207	(33.0)	420	(66.0)	–	–	–	–	–	–	185	(89.4)	20	(9.7)	2	(1.0)	0	(0.0)
	GG 2$^-$	192	0	(0.0)	7.7	(5.4–10.5)	–	–	–	–	–	–	–	–	–	–	124	(64.6)	63	(33.3)	5	(2.6)	0	(0.0)
	GG 2$^+$	**228**	12	(5.2)	8.3	(6.3–14.0)	–	–	228	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	110	(48.2)	90	(39.5)	28	(12.3)	0	(0.0)
	p value (GG 2$^-$ vs GG 2$^+$)		<0.001		0.006														pT3 overall: <0.001					
Hollemans [24]	All (GG 4)	**140**	12	(22.6)	10.0	(7.2–16.0)	–	–	–	–	–	–	140	(100.0)	–	–	67	(47.8)	44	(31.4)	20	(14.3)	1	(0.7)
	GG 4$^-$	53	1	(1.9)	10.0	(7.0–14.0)	–	–	–	–	–	–	–	–	–	–	35	(66.0)	10	(18.9)	8 (15.1)	(pT3b/T4)		
	GG 4$^+$	**87**	11	(20.7)	10.0	(7.5–16.0)	–	–	0	(0.0)	0	(0.0)	87	(100.0)	0	(0.0)	32	(36.8)	34	(39.1)	21 (24.1)	(pT3b/T4)		
	p value		0.05		0.33																		0.003	
Hansum [21]	All (GG 5)	119	17	(14.3)	11.3	(7.1–19.0)	–	–	–	–	–	–	–	–	119	(100.0)	25	(21.0)	48	(40.0)	46	(39.0)	with pT4	
	GG 5$^-$	17	0	(0.0)	10.1	–	–	–	–	–	–	–	–	–	17	(100.0)	9	(52.9)	5	(29.4)	3	(17.6)		
	GG 5$^+$	102	17	(16.7)	18.8	–	–	–	0	(0.0)	0	(0.0)	0	(0.0)	102	(100.0)	16	(15.7)	43	(42.2)	43	(42.2)		
	p value		0.07		0.12																	<0.002		
Kweldam [14]	All (GG 2)	1054	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	GG 2$^+$	**88**	–	–	5.2	(8.7–13.7)	0	(0.0)	88	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	–	–	–	–	–	–	–	–
	GG 2$^-$	282	–	–	4.0	(5.8–8.7)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	RP	146	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	RT	195	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Kweldam [41]	All	1031	–	–	–	–	486	(47.1)	310	(30.1)	104	(10.1)	64	(6.2)	67	(6.5)	–	–	–	–	–	–	–	–
	Cr/ID$^+$	**193**	–	–	–	–	4	(2.0)	54	(28.0)	60	(31.1)	33	(17.1)	42	(21.8)	–	–	–	–	–	–	–	–
	Cr/ID$^-$	838	–	–	–	–	482	(57.5)	256	(30.5)	44	(52.5)	31	(3.7)	25	(3.0)	–	–	–	–	–	–	–	–
Kweldam [23]	All	1055																						
	RP (GG <3)	345	–	–			–	–	–	–	–	–	–	–	–	–								
	GG 1	216	–	–	4.7	(3.5–6.9)	–	–	–	–	–	–	–	–	–	–	187	(87.0)	23	(11.0)	2	(0.93)	1	(0.46)
	GG 2$^-$	112	–	–	5.6	(4.0–7.4)	–	–	–	–	–	–	–	–	–	–	80	(71.0)	11	(65.0)	0		0	
	GG 2$^+$	**17**	–	–	6.4	(4.5–8.8)	–	–	17	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	32	(28.0)	5	(29.0)	0		0	
	p value				0.23 (GG 2$^+$ vs GG 2$^-$)																		>0.5	
	RT	342	–	–			–	–	–	–	–	–	–	–	–	–	cT2			cT3				
	GG 1	188	–	–	5.0	(3.6–7.6)	–	–	–	–	–	–	–	–	–	–	63	(34.)		30	(16.0)			
	GG 2–	120	–	–	5.9	(4.0–9.4)	–	–	–	–	–	–	–	–	–	–	51	(43.0)		29	(24.0)			

Table 2 (*continued*)

Study	Subgroups	Patients	pN+		pre–RP PSA (ng/ml)		GG on RP or biopsy, *n* (%)										pT stage, *n* (%)							
		(*n*)	*n*	(%)	Median	(IQR)	GG 1		GG 2		GG 3		GG 4		GG 5		pT2		pT3a		pT3b		pT4	
	GG 2⁺	**34**	–	–	8.7	(5.1–14)	–	–	34	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	12	(35.0)		15	(44.0)			
	p value				<0.001															>0.1					
Tontilla [37]	All	124	–	–	8.1	(5.5–13.1)	6	(5)	51	(41)	28	(23)	8	(7)	31	(25)	–	–	–	–	–	–	–	–
	All (GG 2)	52	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	GG 2⁺	**31**	–	–	–	–	–	–	31	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)	–	–	–	–	–	–	–	–
	GG 2⁻	21	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Chua [40]	All	1325	–	–	7.1	(5.1–10.5)	272	(29)	423	(4)	172	(19)	65 (7)				–	–	–	–	–	–	–	–
	Cr/ID⁺	**531**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Masoomian et al. [25]	All	245	–	–	7	(0.8–88.5) [b]	29	(12.0)	150	(61.0)	40	(16.0)	18	(7.0)	8	(3.0)	135	(55.0)	74	(30.0)	36	(15.0)	–	–
	Cr/ID⁺	**66**	–	–	7.7	(0.8–88.5) [b]	0	(0.0)	33	(50.0)	18	(27.0)	12	(18.0)	3	(5.0)	24	(3.0)	25	(38.0)	17	(26.0)	–	–
	Cr/ID⁻	179	–	–	6.8	(1.8–50) [b]	29	(16.0)	117	(65.0)	22	(12.0)	6	(3.0)	5	(3.0)	111	(62.0)	49	(27.0)	19	(11.0)	–	–
Trudel [39]	All	246	NS	NS	NS	NS	127	(51.6)	GS 7: 101 (41.1)				GS >7: 18 (7.3)				152	(61.8)	67	(27.2)	27	(11.0)	–	–
	Cr/ID⁺	**80**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cr/ID⁻	166	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Efstathiou [27]	All	115	32	(38.0)	0–4: 13 4.1–10: 42 10.1–20: 27 >20: 33	(11.0) (37.0) (23.0) (29.0)	–	–	14	(12)	19	(17)	82	(71)	–	–	42	(36)	9	(8)	32	(28)	–	–
	Cr/ID⁻	32	–	–	–	–	–	–	GS 7: 10 (31)				22	(69)	–	–	22	(69)	10 (31.0)				–	–
	Cr/ID⁺	**83**	–	–	–	–	–	–	GS 7: 23 (39)				60	(61)	–	–	20	(24)	63 (76.0)				–	–
Downes [36]	All	340	37	(10.9)	–	–	20	(6.0)	144	(42.8)	121	(36.5)	13	(3.9)	36	(10.8)	137	(40.3)		120	(35.3)	83	(24.4)	
	Cr/ID⁺	**203**	35	(17.2)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cr/ID⁻	137	2	(1.5)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Total		**5981**																						
Cribrifo/Intraduct		**2160**	**75**	**(5.2–20.7)**	**– (5.2–18.8)** [b]		**4**	**(0.1)**	**485**	**(60.0)**	**78**	**(9.0)**	**132**	**(16.0)**	**147**	**(17.0)**	**246**	**(39.0)**	**384**	**(61.0)**				
Jang [16]	All men	2648	118	(4.5)	7.8	(5.3–13.4)	2383 (90.0)								265	(10.0)	1201	(45.4)	1149	(43.3)	298 (11.3)			
	Acinar	2547	104	(4.1)	7.7	(5.2–13.1)	2310 (90.7)								237	(9.3)	1174	(46.1)	1102	(43.3)	271 (10.6)			
	Ductal	**101**	14	(13.9)	11.9	(7.4–26.7)	73 (72.3)								28	(27.7)	27	(26.7)	47	(46.6)	27 (26.7)			
	p value		<0.001	–	<0.001	–	0.264										p <0.001							
	Ductal <30%	22	3	(13.6)	8.0	(6.2–19.1)	16 (72.7)								6	(27.3)	9	(40.9)	5	(22.7)	8 (36.4)			
	Ductal ≥30%	79	11	(13.9)	14.4	(8.1–28.0)	57 (72.2)								22	(27.8)	18	(22.7)	42	(53.2)	19 (24.1)			
	p value	–	>0.999	–	0.139	–	0.226										p = 0.038							
Samaratunga [32]	All	268	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Acinar	234	–	–	7.2 [a]	(2.2–37.0) [b]	36	(15.4)		174	(74.4)		24 (10.3)				157	(67.1)		77	(32.9)		–	–
	Ductal	**34**	0	(0)	8.4 [a]	(0.8–21.0) [b]	0	(0)		12	(35.3)		22 (64.7)				9	(26.5)		25	(73.5)		–	–
Kim [17]	Acinar	116	3	(10.3)	16.2 [a]	±17.6 [f]	62 (53.5)						54 (46.5)				47 (40.6)		69 (59.4)					
	Ductal	**29**	11	(9.4)	14.7 [a]	±14.2 [f]	10 (34.5)						19 (65.5)				13 (44.9)		16 (55.1)					

(*continued on next page*)

Table 2 (*continued*)

Study	Subgroups	Patients	pN+		pre–RP PSA (ng/ml)		GG on RP or biopsy, *n* (%)										pT stage, *n* (%)							
		(*n*)	*n*	(%)	Median	(IQR)	GG 1		GG 2		GG 3		GG 4		GG 5		pT2		pT3a		pT3b		pT4	
	p value		0.873		0.998	–							0.024						0.694					
Jeong [18]	**Ductal**	**61**	3	4.9	11.7	(0.6–66.4) [b]	–	–	–	–	–	–	–	–	–	–	17	(27.9)	29	(47.5)	15	(24.6)	0	(0.0)
Vinceneux [34]	**Ductal**	**45**	6	(13.3)	7.3	(1.4–63) [b]	–	–	–	–	–	–	31	(68.8)	12	(26.6)	15	(33.3)	16	(35.6)	14	(31.1)	–	–
	High-grade acinar	5	–	–	8.1	(2.2–52) [b]	–	–	–	–	–	–		–	–	–	–	–	–	–	–	–	–	–
Chow [28]	**Ductal**	**202**			8.3	(6.0–12.0)	0	(0.0)	28	(13.9)	89	(44.1)	27	(13.4)	58	(28.7)	37	(18.3)	116	(57.4)	47	(23.3)	2	(1.0)
	Acinar	2037			6.4	(4.9–9.0)	0	(0.0)	1211	(59.5)	576	(28.3)	81	(4.0)	169	(8.3)	1242	(61.0)	625	(30.7)	170	(8.3)	0	(0.0)
	p value					0.02									<0.001								<0.001	
	MP ductal	186	–	–	8.4	(6.0–12.0)	0	(0.0)	26	(14.0)	85	(45.7)	22	(11.8)	53	(28.5)	35	(18.8)	106	(56.9)	44	(23.6)	1	(0.5)
	MP acinar	186	–	–	8.7	(6.3–13.0)	0	(0.0)	26	(14.0)	88	(47.3)	21	(11.3)	51	(27.4)	37	(18.3)	92	(49.5)	57	(30.6)	0	(0.0)
	p value				0.046										0.99								0.59	
Harkin [29]	**Ductal**	**68**	5	(7.4)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Acinar	72	0	(0.0)	–	–	–	–	–	–	–	–	GG ≥4: 72				–	–	–	–	–	–	–	–
	p value			0.03	–	NA										NA							<0.001	
Tan [19]	**Ductal**	**79**	12	(15.2)	12.5	(2.8–86.4)	0	(0.0)	25	(31.6)	33	(41.8)	13	(16.5)	8	(10.1)	26	(32.9)	29	(36.7)	24	(30.4)	–	–
	Acinar	948	41	(4.3)	10.8	(1.2–87.2)	143	(15.1)	521	(55.0)	195	(20.6)	45	(4.7)	44	(4.6)	667	(70.3)	178	(18.8)	103	(10.9)	–	–
	p value		<0.001		0.034										<0.001				<0.001		<0.001			
Total		**6578**																						
Ductal		**619**	**51**	**(0.0–15.2)**	**8.3–14.7**		**0**	**(0.0)**	**GS 7: 187 (64.0)**				**GS >7: 106 (36.0)**				**116**	**(20.0)**	**>pT2: 459 (80.0)**					
Kato [45]	All	145	–	–	33.2	(2.4–296) [b]	9	(6)	27 (19)				40	(28)	69	(48)	–	–	–	–	–	–	–	–
	IDC⁻	92	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	IDC disappear [c]	**15**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	IDC persist [c]	**38**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Kato [46]	IDC⁻	130	–	–	≤20: 46 >20: 84	(35.0) (65.0)	<5 87 (67.0)								43	(33.0)	–	–	–	–	–	–	–	–
	IDC⁺	**74**	–	–	≤20: 37 >20: 37	(50.0) (50.0)	<5 65 (88.0)								9	(12.0)	–	–	–	–	–	–	–	–
	p value				0.0537											0.0008								
Kato [43]	All	1019	–	–	6.8	(0.4–82) [b]	–	–	–	–	–	–	–	–	–	–	743	/72.9)	234	(22.9)	42	(4.1)	0	(0.0)
	IDC⁻	862	–	–	–	–	163	(16.0)	470	(94.2)	160	(72.7)	27	(67.5)	42	(43.3)	–	–	–	–	–	–	–	–
	IDC⁺	**157**	–	–	–	–	0	(0.0)	29	(5.8)	60	(27.3)	13	(32.5)	55	(56.7)	–	–	–	–	–	–	–	–
Karakoc [59]	All	67	–	–	–	–	Only mean GS reported										32	(48)	35	(52)	0	(0)	0	(0)
	pT3a + NSM IDC⁻	30	–	–	8.8 [a]	±5.1 [f]	GS 7 [a] ± 0.4 [f]										0	(0)	30	(100)	0	(0)	0	(0)
	pT3a + NSM IDC⁺	**5**	–	–	9 [a]	±3.5 [f]	GS 7.2 [a] ± 0.4 [f]										0	(0)	5	(100)	0	(0)	0	(0)
	pT2 + PSM IDC⁻	28	–	–	7.6 [a]	±3.4 [f]	GS 6.7 [a] ± 0.4 [f]										28	(100)	0	(0)	0	(0)	0	(0)
	pT2 + PSM IDC⁺	**4**	–	–	9.2 [a]	±5.5 [f]	GS 7 [a] ± 0 [f]										4	(100)	0	(0)	0	(0)	0	(0)
O'Brien [42]	All	1939	13	(1.7)	6.7	(0.1–59.2) [b]	409	(21.1)	923	(47.6)	494	(25.5)	113 (5.8)								pT3b/4: 97 (5)			

Table 2 (*continued*)

Study	Subgroups	Patients	pN+		pre–RP PSA (ng/ml)		GG on RP or biopsy, *n* (%)										pT stage, *n* (%)							
		(*n*)	*n*	(%)	Median	(IQR)	GG 1		GG 2		GG 3		GG 4		GG 5		pT2		pT3a		pT3b		pT4	
	IDC⁺	**363**	–	–	–	–		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Van der Kwast [44]	Cohort 1 (PMH)	118	–	–	7.9	(1.3–19.3) [b]	38	(32)	80 (68)				0	(0)	0	(0)	≤cT2: 118 (100)				–	–	–	–
	Cohort 1 IDC	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cohort 1 IDC⁺	**23**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cohort 2 (EORTC)	135	–	–	<4:4 4–10: 16 10–20: 20 >20: 81	(3.0) (12.0) (15.0) (60.0)	12	(9)	75 (58)				30	(23)	13	(10)	6	(4)	116 (86)				13	(10)
	Cohort 2 RT IDC⁻	50	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cohort 2 RT IDC +	**19**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cohort 2 RT + ltAD IDC⁻	52	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cohort 2 RT + ltAD IDC⁺	**11**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Miyai [20]	HGPIN	436	2	(1)	>10 ng/ml: 33 (8.0)		401 (92)						35 (8)				399	(92)	37 (8)					
	ACL	22	0	(0)	2	(9.0)	15 (68)						7 (32)				17	(77)	5 (23)					
	IDC⁺	**155**	16	(11)	21	(14.0)	79 (51)						76 (49)				79	(51)	76 (49)					
Zhu [15]	All	418	–	–	17.4	(10.0–35.5)	60	(14.4)	130	(31.1)	101	(24.2)	4	(11.5)	79	(18.9)	141	(33.7)	183	(43.8)	81	(19.4)	13	(3.1)
	IDC⁻	382	–	–	16.7	(9.82–29.78)	60	(15.7)	129	(33.8)	9	(25.1)	45	(11.8)	52	(13.6)	36	(35.6)	173	(45.3)	62	(16.2)	11	(2.9)
	IDC⁺	**36**	–	–	33.6	(14.5–78.1)	0	(0.0)	1	(2.8)	5	(13.9)	3	(8.3)	27	(75.0)	9	(13.9)	10	(27.8)	19	(52.8)	2	(5.6)
	p value					0.03									<0.001								<0.001	
	IDC⁻ matched	108	–	–	24.8	(15.77–NA)	1	(0.9)	9	(8.3)	21	(19.4)	25	(23.1)	52	(48.1)	43	(39.8)	65	(60.2)	>pT2			
	IDC⁺	36	–	–	33.6	(14.5–78.1)	0	(0.0)	1	(2.8)	5	(13.9)	3	(8.3)	27	(75.0)	9	(13.9)	10	(27.8)	19	(52.8)	2	(5.6)
	p value					0.491									0.072				0.558					
Trinh [35]	**IDC⁺** (CRC) [d]	**65**	9	(13.8)	9.2 [a]	±15.1 [f]	1	(1.5)	11	(16.9)	31	(47.7)	4	(6.2)	1	(27.7)	–							
	IDC⁻ (CRC)	20	1	(5.0)	10.1 [a]	±5.8 [f]	6	(30.0)	5	(25.0)	6	(30.0)	2	(10.0)	18	(5.0)								
	p value		0.551		0.694										<0.001						0.063			
Trinh [30]	All	293	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–					–	–
	High risk																							
	RP + aRT, IDC+	**21**	–	–	–	–	0	(0)	7	(33)	8	(38)	1	(5)	5	(24)	1	(5.0)	11	(52.0)	9	(43.0)	–	–
	RP + aRT, IDC⁻	27	–	–	–	–	2	(7)	15	(56)	7	(26)	0	(0)	3	(11)	4	(15.0)	16	(59.0)	7	(26.0)	–	–
	RP only, IDC⁺	**33**	–	–	–	–	8	(24)	10	(30)	11	(33)	1	(3)	3	(9)	11	(33.0)	16	(48.0)	6	(18.0)	–	–
	RP only, IDC–	64	–	–	–	–	26	(41)	31	(48)	4	(6)	1	(2)	2	(3)	41	(64.0)	16	(25.0)	7	(11.0)	–	–
	p value						<0.001												0.026		0.013			
	Not high risk																							
	RP only, IDC⁺	**19**	–	–	–	–	8	(42)	9	(47)	2	(11)	0	(0)	0	(0)	19	(100.0)	0	(0)	0	(0)	–	–
	RP only, IDC⁻	129	–	–	–	–	85	(66)	36	(28)	8	(6)	0	(0)	0	(0)	129	(100.0)	0	(0)	0	(0)	–	–
	p value						0.134																	
Total Intraductal		**1732** **246**	**25**	**(11.0)**	**– (9.2–33.6)**		**16**	**(6.0)**	**56**	**(21.1)**	**86**	**(32.3)**	**18**	**(6.8)**	**90**	**(33.8)**	**40**	**(56.0)**	**10**	**(14.0)**	**19**	**(27.0)**	**2**	**(3.0)**

(*continued on next page*)

Table 2 (*continued*)

Study	Subgroups	Patients	pN+		pre–RP PSA (ng/ml)		GG on RP or biopsy, *n* (%)										pT stage, *n* (%)							
		(*n*)	*n*	(%)	Median	(IQR)	GG 1		GG 2		GG 3		GG 4		GG 5		pT2		pT3a		pT3b		pT4	
Kweldam [26]	GS 7 at RP	535	–	–	6.4	(4.2–10)	0	(0.0)	436	(81.0)	99	(19.0)	0	(0.0)	0	(0.0)	270	(50.0)	218	(41.0)	47	(8.8)	–	–
	Mets/PCM^{+}	52	11	(21.0)	7.8	(5.3–13	0	(0.0)	27	(52.0)	25	(48.0)	0	(0.0)	0	(0.0)	10	(19.0)	25	(48.0)	17	(33.0)	–	–
	Mets/PCM^{-}	109	0	(0.0)	7.4	(5.4–16)	0	(0.0)	88	(81.0)	21	(19.0)	0	(0.0)	0	(0.0)	22	(20.0)	61	(56.0)	26	(24.0)	–	–
	p value				0.60						0.001										0.48			
	Cr+	**83**	–	–	8.1	(5.4–17)	0	(0.0)	48	(58.0)	35	(42.0)	0	(0.0)	0	(0.0)	14	(17.0)	43	(52.0)	26	(31.0)	–	–
	Cr^{-}	78	–	–	7.1	(5.2–12)	0	(0.0)	67	(86.0)	11	(14.0)	0	(0.0)	0	(0.0)	18	(23.0)	43	(55.0)	17	(22.0)	–	–
	p value					0.15					<0.001										0.33			
Leo [48]	All men	749	27	(3.6)	6	(5–9)	146	(19.5)	356	(47.5)	139	(18.6)	48	(6.4)	47	(6.3)	325	(43.4)	207	(27.6)	81	(10.4)	2	(0.3)
	CAI ≤0.10 [e]	591	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	CAI >0.10	**158**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Keefe [31]	All men	104	–	–	7.5 [a]	±4.2 [f]	0	(0.0)	76	(73)	27	(26)	0	(0.0)	1	(1)	58	(55.8)	40	(38.5)	6	(5.8)	0	(0)
	Cr+	**30**	–	–	–	–	–	–	–	–	GS >7: 11 (36.7)						–	–	pT3: 18 (60)				–	–
Kir [49]	All men	233	–	–	–	–	109	(46.8)	85	(36.5)	26	(11.7)	0	(0.0)	13	(5.6)	169	(72.5)	T3: 64 (27.5)				0	(0.0)
Choy [50]	All men	585	–	–	–	–	235	–	287	–	63	–	0	(0.0)	0	(0.0)	487	(83.2)	78	(13.3)	20	(3.4)	0	(0.0)
Greenland [47]	**ExCr**	**52**	5	9.6	–	–	0	(0.0)	30	(58)	22	(42)	0	(0.0)	0	(0.0)	–	–	–	–	–	–	–	–
	GA	58	0	0	–	–	0	(0.0)	47	(81)	11	(19)	0	(0.0)	0	(0.0)	–	–	–	–	–	–	–	–
Total		**1942**																						
Cribriform		**323**	**5**	**(9.6)**	**8.1**		**0**	**(0.0)**	**78**	**(58.0)**	**57**	**(42.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**14**	**(17.0)**	**43**	**(52.0)**	**26**	**(31.0)**		
Osunkoya [58]	**Mucinous**	**47**	–	–	9	(1.9–34.3) [b]	6	(12.8)	31	(78.7)	6	(12.8)	4	(8.5)	0	(0.0)	27	(57.5)	20	(42.5)	–	–	–	–
Samaratunga [33]	**Mucinous**	**143**	1	(2.8)	7.8	(2.5–25.2) [b]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	≤25% inv.	70	–	–	6.60	(4.45–9.58) [b]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	>25% inv.	73	–	–	7.10	(5.30–8.90) [b]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Matched NM	143	–	–	5.65	(4.5–7.3) [b]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Total		**333**																						
Mucinous		**190**	**1**	**(2.8)**	**(7.8–9)**		**6**	**(12.8)**	**31**	**(78.7)**	**6**	**(12.8)**	**4**	**(8.5)**	**0**	**(0.0)**	**27**	**(57.5)**	**20**	**(42.5)**	**–**	**–**	**–**	**–**
Tavora [51]	**All**	**28**	–	–	5.9 [a]	(1.2–12.1) [b]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	RP	9	0	(0)	–	–	6	(66)	–	–	–	–	–	–	–	–	8	(89)	1	(11)	–	–	–	–
	Hormonal therapy	7	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Radiotherapy	5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cryotherapy	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

ACL = atypical cribriform lesion; aRT = adjuvant RT; CAI = cribriform area index; CRC = clinically recurrent; Cr/ID = cribriform or ductal carcinoma; EORTC = European Organization for Research and Treatment of Cancer; ExCr = expansile cribriform; GA = glomeruloid architecture; GG = International Society of Urological Pathology grade group; HGPIN = high-grade PIN; IDC = intraductal carcinoma; inv. = involvement; ltAD = long-term androgen deprivation; Mets/PCM = metastases or prostate cancer mortality; MP = matched pair; NA = not available; NM = nonmucinous; NSM = negative surgical margin; IQR = interquartile range; PCa = prostate cancer; PIN = prostatic intraepithelial neoplasia; PMH = Princess Margaret Hospital; PSA = prostate-specific antigen; PSM = positive surgical margin; RP = radical prostatectomy; RT = radiotherapy.

Note: Table 2 Due to graphical issues some columns including Age and Positive Surgical Margins are available in the online format only as a supplementary file, and not in the printed version.

[a] Mean.

[b] Range.

[c] Disappear = positive at biopsy, negative at RP; persistence = positive at biopsy and at RP.

[d] Data from Leo et al. were considered as cribriform-negative in cases with CAI <10.

[e] Not considered among the total number of cases.

[f] ±standard deviation.

Table 3 – Oncological outcomes in the retrospective series[†]

Study	Subgroups	Follow-up (mo)		BCR						Multivariable analysis				Metastasis-free survival						Multivariable analysis		
		Median	(IQR)	*n*	(%)	Outcome	Time (yr)	Survival (%)	(95% CI)	Ref.	HR	(95% CI)	*p* value	*n*	%	Outcome	Time (yr)	Survival (%)	95% CI	HR	95% CI	*p* value
Hollemans [38]	All PCa	53.8	(15.6–104.8)	126	(15.1)	–	–	–	–	–	–	–	–	33	(3.9)	–	–	–	–	–	–	–
	Cr/ID			–	–	–	–	–	–	GG 1	**1.7**	**(1.0–2.9)**	**0.006**	**7**	**(1.7)**	–	–	–	–	–	–	–
Hollemans [22]	All men (GG 1–2)	59.6	(17.5–113.9)	112	–	–	–	–	–	–	–	–	–	13	(2.0)	–	–	–	–	–	–	–
	GG 1			16	(8.0)	–	15	>90 [b]		–	–	–	–	0	(0.0)	–	–	–	–	–	–	–
	GG 2^{-}			29	(15.0)	–	15	>90 [b]		–	–	–	–	0	(0.0)	–	–	–	–	–	–	–
	GG2^{+}			**67**	**(29.0)**	–	**15**	**80–90** [b]		GG 1	**3.0**	**(1.4–6.3)**	**0.004**	**13**	**(5.7)**	–	–	–	–	–	–	–
	p value							<0.001							NA							
Hollemans [24]	All men (GG 4)	68.7	(36.7–102.8)	68	(49.0)	–	–	–	–	–	–	–	–	36	(26.0)	–	–	–	–	–	–	–
	GG 4^{-}			16	(30.2)	–	–	–	–	–	–	–	–	4	(7.5)	–	–	–	–	Ref	–	–
	GG 4^{+}			**52**	**(59.8)**	–	–	–	–	Cr/ID^{-}	**2.0**	**(1.0–3.7)**	**0.04**	**32**	**(36.8)**	–	–	–	–	**3.5**	**(1.0–12.3)**	**0.05**
	p value			0.001										<0.001								
Hansum [21]	All men (GG 5)			77	(65.0)	–	–	–	–	–	–	–	–	47	(39.0)	–	–	–	–	–	–	–
	GG 5^{-}			2	(11.8)	–	–	–	–	–	–	–	–	0	(0.0)	–	–	0	–	Ref	–	–
	GG 5^{+}			**75**	**(73.5)**	–	–	**–**	–	Cr/ID^{-} (all GGs)	**2.1**	**(1.5–2.9)**	**<0.001**	**47**	**(46.1)**	–	–	**46.1**	–	**9.9**	**(3.9–25.5)**	**<0.001**
	p value			<0.001														0.002				
Kweldam [14]	RP (GG 2$^{+/-}$)	15.5 yr	(14.0–17.2)	35	(24.0)	BCR [a]		–	–	GG 2^{-}	**2.4**	**(1.03–5.60)**	**0.04**	–	–	–	–	–	–	–	–	–
	RT (GG 2$^{+/-}$)	13.1 yr	(8.4–15.9)	72	(36.9)	BCR [a]		–	–	GG 2^{-}	**1.2**	**(0.68–2.13)**	**0.53**	–	–	–	–	–	–	–	–	–
Kweldam [41]	All men	13 yr	(9.4–16)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cr/ID^{-}			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cr/ID+			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Kweldam [23]		15 yr	(10–17 yr)																			
	RP													–	–	–	–	–	–	–	–	–
	GG 1			27	(13.0)	BCRFS	15	87.0	(82.0–92.0)	Ref.	Ref.	Ref.	Ref.	–	–	–	–	–	–	–	–	–
	GG 2^{-}			22	(20.0)	BCRFS	15	NA; similar to GG 1 $p = 0.13$			1.3	(0.67–2.4)	0.47	–	–	–	–	–	–	–	–	–
	GG 2^{+}			**6**	**(35.0)**	BCRFS	**15**	**NA; lower $p = 0.002$**			**3.0**	**(1.1–7.8)**	**0.03**	–	–	–	–	–	–	–	–	–
	p value				.																	
	RT																					
	GG 1			33	(18.0)		15	78.0	(72.0–85.0)	Ref.	Ref.	Ref.	Ref.	–	–	–	–	–	–	–	–	–
	GG 2^{-}			32	(27.0)		15	NA; higher $p = 0.04$			0.88	(0.51–1.5)	0.63	–	–	–	–	–	–	–	–	–
	GG 2^{+}			**16**	**(47.0)**		**15**	**NA; higher $p = 0.01$**			**1.2**	**(0.58–2.3)**	**0.67**	–	–	–	–	–	–	–	–	–
	p value				–																	
Tontilla [37]	All GG 2	29	(24–34)	13	(25)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	GG 2^{+}			11	(35.5)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	GG 2^{-}			2	(9.5)	–	–	–	–	–	–	–	**–**	–	–	–	–	–	–	–	–	–
Chua [40]	**All men**	5.7–71.1 yr		238.00	(26.0)									52	(6.0)	–	–	–	–	–	–	–

(*continued on next page*)

Study	Subgroups	Follow-up (mo)		BCR						Multivariable analysis				Metastasis-free survival						Multivariable analysis		
		Median	(IQR)	*n*	(%)	Outcome	Time (yr)	Survival (%)	(95% CI)	Ref.	HR	(95% CI)	*p* value	*n*	%	Outcome	Time (yr)	Survival (%)	95% CI	HR	95% CI	*p* value
	Cr/ID$^+$									Cr/ID$^-$	**2.04**	**(1.34–3.09)**	**<0.001**	–	–	–	–	–	–	**3.31**	**(1.76–6.21)**	**<0.001**
Trudel [39]	All	10.6	(1.5–175.3) [f]	61	(26.0)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cr/ID$^+$			–	–	–	–	–	–	–	**2.98**	**(1.69–5.28)**	**0.00018**	–	–	–	–	–	–	–	–	–
	Cr/ID–			–	–	–	–	–	–	–	Ref.		–	–	–	–	–	–	–	–	–	–
Efstathiou [27]	All men	4.1 yr	(0.7–8.9 yr) [f]	42	(37)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cr/ID–			4	(29)	–	–	–	–	–	Ref.		–	–	–	–	–	–	–	–	–	–
	Cr/ID$^+$			**38**	**(46)**	–	–	–	–	–	**2.98**	**SE 0.32**	**0.02**	–	–	–	–	–	–	–	–	–
Cribrifo/ Intraduct$^+$											*n* = 8 S*									*n* = 3 S*		
											n = 1 NS											
		–	–	216	(46.3)						*n* = 1 S* for RP, NS for RT			92	(27.9)							
Jang [16]	All men	66	(41–85)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Acinar			–	–	BCR	5	28.4	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Ductal			–	–	**BCR**	**5**	**70.5**	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	p value			–	–	–	–	<0.0001	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Ductal <30%			–	–	–	–	–	–	–	1.435	(0.709–2.903)	0.315	–	–	–	–	–	–	–	–	–
	Ductal ≥30%			–	–	–	–	–	–	–	**2.933**	**(2.199–3.913)**	**<0.001**	–	–	–	–	–	–	–	–	–
	p value			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Kim et al. [17]	Acinar	58 [g]	±10.5 [h]	20	(16.6)	BCR	5	80.0 [c]	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Ductal	23.8 [g]	±20.6 [h]	**10**	**(34.4)**	**BCR**	**5**	**60.0** [c]	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	p value			–	–	–	–	0.016	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Jeong [18]	**Ductal**	19.3	(1–70)	**26**	**(42.6)**		**10.5 mo**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Vinceneux [34]	**Ductal**	27	(0–177)	**19**	**(42.0)**	BCR	–	–	–	–	–	–	–	**12**	**(26.6)**	–	–	–	–	–	–	–
Chow [28]	**Ductal**	18.4	(8.5–33.3)	**84**	**(41.8)**						**1.57**	**(1.2–2.05)**	**<0.01**	**52**	**(25.9)**							
	Acinar	32.6	(12.4–63.0)								Ref.											
	p value																					
	MP ductal	18.1	(8.48–31.08)	**77**	**(41.4)**		**10**	**NA**						**48**	**(25.8)**	MFS	10					
	MP acinar	103.2	(47.18–142.62)	140	(75.2)		10	NA						63	(33.8)	MFS	10					
	p value	<0.001						>0.5									0.001					
Harkin [29]	**Ductal**	50		**37**	**(55.2)**						**1.09** [d]	**(1.01–1.18)**	**0.03**									
	Acinar	58.5		27	(37.5)						Ref.											
	p value	0.38		<0.01																		
Tan [19]	All men	85.6 [g]	(36.3–136)																			
	Ductal			**31**	**(39.2)**						**1.918**	**(1.074–3.423)**	**0.028**									
	Acinar			115	(12.5)																	
	p value			0.034					–	–				–	–	–	–	–	–	–	–	–
Ductal											*n* = 4 S*											
		–	–	207	(42.9)									112	(25.9)							
Kato et al. [45]	All men	109	(11–257) [f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 3 (*continued*)

Study	Subgroups	Follow-up (mo)		BCR						Multivariable analysis				Metastasis-free survival						Multivariable analysis		
		Median	(IQR)	*n*	(%)	Outcome	Time (yr)	Survival (%)	(95% CI)	Ref.	HR	(95% CI)	*p* value	*n*	%	Outcome	Time (yr)	Survival (%)	95% CI	HR	95% CI	*p* value
	IDC⁻			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	IDC disappear [e]			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	IDC persist [e]			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Kato et al. [46]	All men	108	(11–257) [f]	–	–	–	–	–	–	–	–	–	–	48	(23.5)	–	–	–	–	–	–	–
	IDC⁻			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	IDC⁺			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	p value																					
Kato et al. [43]	All men	82	(0.7–148)	–	–	–	–			–	–	–	–	–	–	–	–	–	–	–	–	–
	IDC⁻			–	–	–	–	–	–	–	Ref.	–	–	–	–	–	–	–	–	–	–	–
	IDC⁺			–	–	–	–	–	–	–	**2.17**	**(1.58–2.98)**	**<0.01**	–	–	–	–	–	–	–	–	–
Karakoc et al. [59]	All men			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	pT3a + NSM IDC⁻	48 [g]	±35.1 [h]	0	(0)	BCRFS	1	NA	–	–	–	–		–	–	–	–	–	–	–	–	–
	pT3a + NSM IDC⁺			**3**	**(60)**	**BCRFS**	**1**	**NA**		–	–	–	–	–	–	–	–	–	–	–	–	–
	p value			0.002			<0.001															
	pT2 + PSM IDC⁻	63 [g]	±43.6 [h]	7	(25)	BCRFS	1	NA	–	–	–	–		–	–	–	–	–	–	–	–	–
	pT2 + PSM IDC⁺			**3**	**(75)**	**BCRFS**	**1**	**NA**	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	p value			>0.05			<0.005															
O'Brien et al. [42]	**IDC**	NA		–	–	–	–		–	IDC⁻	1.72	–	<0.0001	–	–	–	–	–	–	–	–	–
Van der Kwast et al. [44]	Cohort 1 (PMH)	78	(9.6–124.8) [f]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cohort 1 IDC⁻			–	–	–	–	–	–	–	Ref.	–	–	–	–	–	–	–	–	–	–	–
	Cohort 1 IDC⁺			–	–	–	–	–	–	–	**0.44**	**(0.10–1.91)**	**0.27**	–	–	–	–	–	–	–	–	–
	Cohort 2 (EORTC)	109.2	(61.2–151.2)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Cohort 2 RT IDC⁻			–	–	–	–	–	–	–	–	–	–	–	–	MFS	3	89.9	(81.6–98.3)	Ref		
	Cohort 2 RT IDC⁺			–	–	–	–	–	–	–	–	–	–	–	–	**MFS**	**3**	**42.1**	**(19.9–64.3)**	**5.28**	**(2.4–11.4)**	**<0.001**
Miyai et al. [20]	All	17	(1–86) [f]	62	(7)																	
	IDC⁻					BCRFS	3	99.6			Ref.											
	IDC⁺					**BCRFS**	**3**	**90.0**			**17.97**	**(2.47–130.46)**	**0.0043**									
	p value							<0.001														
Zhu et al. [15]	All men			79	(18.9)	BCR	5	41.0						–	–	–	–	–	–	–	–	–
	IDC⁻			64	(16.8)	BCR	–	–			Ref.			–	–	–	–	–	–	–	–	–
	IDC⁺			**15**	**(41.7)**	BCR	–	–			**2.415** **2.299** **2.821**	**(1.238–4.711)** **1.019–5.183**	**0.010** **0.045** **0.020**	–	–	–	–	–	–	–	–	–

(*continued on next page*)

Table 3 (*continued*)

Study	Subgroups	Follow–up (mo)		BCR						Multivariable analysis				Metastasis-free survival						Multivariable analysis		
		Median	(IQR)	*n*	(%)	Outcome	Time (yr)	Survival (%)	(95% CI)	Ref.	HR	(95% CI)	*p* value	*n*	%	Outcome	Time (yr)	Survival (%)	95% CI	HR	95% CI	*p* value
												1.178–6.758										
	IDC⁻ matched										Ref.			–	–	–	–	–	–	–	–	–
	IDC⁺ matched										**2.17**	**(1.13–4.18)**	**0.02**	–	–	–	–	–	–	–	–	–
Trinh et al. [35]	**IDC⁺**	109.5	±55.9 [h]	–										–	–	–	–	–	–	**6.27**	**(1.43–27.6)**	**0.015**
	IDC⁻	120.8	±49.4 [h]																	Ref.		
Trinh et al. [30]	All men	99	(53–136)	69	(23.5)	–	–	–	–	DC⁻	**2.39**	**(1.44–3.97)**	**0.001**	–	–	–	–	–	–	–	–	–
	RP + aRT, IDC⁺	49	(30–67)	–	–	–	–	–		–	–	–	–	–	–	–	–	–	–	–	–	–
	RP + aRT, IDC⁻	44	(23–65)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	RP only, IDC⁺	61	(24–123)	–	–	–	–	–		–	–	–	–	–	–	–	–	–	–	–	–	–
	RP only, IDC⁻	108	(56–153)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	p value	<0.001		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	RP only, IDC⁺	89	(61–116)	–	–	**BCR**	**10**	**37.0**		–	**3.24**	**(1.20–8.77)**	**0.021**	–	–	–	–	–	–	–	–	–
	RP only, IDC⁻	118	(84–139)	–	–	BCR	10	10.0			Ref.	–	–	–	–	–	–	–	–	–	–	–
	p value	0.685		–	–	–	0.002	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Total											*n* = 5 S*									*n* = 2 S*		
Intraductal				21	(46.6)						*n* = 1 NS			–	–							
Kweldam et al. [26]	**Cr+**	120	(73–170)	–	–	–			–		**2.0**	**(1.2–3.4)**	**0.006**	–	–					**8.0**	**(3.0–21)**	**<0.001**
	Cr⁻	150	(120–180)	–	–	–			–		Ref.		–	–	–					Ref		–
	p value		0.012				<0.001										<0.001					
Leo et al. [48]	All men	28	(15–62)	177	(23.6)				–					–	–	–	–	–	–	–	–	–
	Cr ≤10%			–	–	–	–	–	–		Ref.			–	–	–	–	–	–	–	–	–
	Cr >10%			–	–	–	–	–	–		**1.65**	**(1.13–2.40)**	**0.0025**	–	–	–	–	–	–	–	–	–
Kir et al. [49]	All men	33.47	±16.08 [h]			–	–	–	–					–	–	–	–	–	–	–	–	–
	Cr⁺			**26**	**(18.0)**						**11.92**	**(1.58–89.72)**	**0.016**	–	–	–	–	–	–	–	–	–
	Cr⁻			4	(4.3)						Ref.			–	–	–	–	–	–	–	–	–
Choy et al. [50]	All men	74	(42–85)	–	–	–								–	–	–	–	–	–	–	–	–
	Cr⁺			–		**BCRFS**	**5**	**68**	**(59–76)**		**1.78**	**1.08–2.92**	**0.02**	–	–	–	–	–	–	–	–	–
	Cr⁻			–		BCRFS	5	85	(78–89)		Ref.			–	–	–	–	–	–	–	–	–
Greenland [47]	**ExCr⁺**	360.5 d		–	–	**BCRFS**	**2**	**59**	–		**4.1**	**0.77–21.5**	**0.098**	–	–	–	–	–	–	–	–	–
	Cr⁻ (GA)	407 d		–	–	BCRFS	2	96	–		Ref.		–	–	–	–	–	–	–	–	–	–
	p value			26	(18.0)			0.02						–	–							
Total											*n* = 5 S*									*n* = 1 S*		
Cribriform																						
Osunkoya [58]	**Mucinous**	6	(1–15)	**1**	**(2.1)**	**BCRFS**	**5**	**97.2**	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Samaratunga [33]	**Mucinous**	38 [g]	(18–72) [f]	**17**	**(11.8)**	**BCR**	**5**	**12.5**						–	–	–	–	–	–	–	–	–

Table 3 (*continued*)

Study	Subgroups	Follow-up (mo)		BCR					Multivariable analysis				Metastasis-free survival					Multivariable analysis		
		Median	(IQR)	*n*	(%)	Outcome	Time (yr)	Survival (%)	(95% CI)	Ref.	HR	(95% CI)	*p* value	*n*	%	Outcome	Time (yr)	Survival (%)	95% CI	HR	95% CI	*p* value
	Mucinous[a] MP			24	(16.8)	BCR	5	17						–	–	–	–	–	–	–	–	–
Mucinous		6–38		18	(9.4)																	
Tavora et al. [51]	All men	5	(1–32)[f]	**0**	**(0)**		–	–	–	–	–	–	–	**0**	**(0)**	–	–	–	–	–	–	–

aRT = adjuvant RT; BCR = biochemical recurrence; BCRFS = BCR-free survival; CI = confidence interval; Cr/ID = cribriform or ductal carcinoma; CSD = cancer-specific death; CSS = cancer-specific survival; EORTC = European Organization for Research and Treatment of Cancer; ExCr = expansile cribriform; GA = glomeruloid architecture; GG = International Society of Urological Pathology grade group; IDC = intraductal carcinoma; MFS = metastasis-free survival; MP = matched pair; NA = not available; NM = nonmucinous; NS = nonsignificant; NSM = negative surgical margin; IQR = interquartile range; PCa = prostate cancer; PIN = prostatic intraepithelial neoplasia; PMH = Princess Margaret Hospital; PSM = positive surgical margin; Ref. = reference; RP = radical prostatectomy; RT = radiotherapy; S* = significant; SE = standard error.

Note: Table 3 Due to graphical/space-related issues some columns including Cancer Specific Deaths, and All Cause Deaths are available in the online format only as a supplementary file, and not in the printed version.

[†] Results from Masoomian et al. [25], Samaratunga et al. [32] (ductal PCa: odds ratio 2.760; $p = 0.00001$), and Keefe et al. [31] are not presented in the table as the only outcome described was pathological stage at RP. On results are presented for overall survival, as none of the studies reported details for this outcome.

[a] Whole cohort.

[b] Kaplan-Meier survival plots were available but survival was not precisely stated.

[c] Kim et al. [17] reported a figure with Kaplan-Meier survival estimates for BCR but precise numbers were not reported; Hence the rates reported in this table are an approximation derived from the figure and do not precisely reflect the statistical results.

[d] Harkin et al. [29] assessed percentage ductal carcinoma as a continuous variable in multivariable analysis.

[e] Disappear = positive at biopsy, negative at RP; persistence = positive at biopsy and at RP.

[f] Range.

[g] Mean.

[h] ±standard deviation.

undergoing treatment with curative intent, we systematically reviewed the available evidence on this topic. Several findings are noteworthy.

First, although no major differences in baseline diagnostic characteristics were observed between the UH and conventional PCa cohorts, UH presence was associated with worse pathological features. For example, more than half of the UH cases had GS 7 PCa. However, EPE was reported in more than 60% of UH. Multivariable analyses confirmed the association between UH and advanced pathological stages in several series. Interestingly, this rarely translated into higher PSM rates. Despite scarce information on the type of lymphadenectomy performed, LNI was relatively frequent among UH patients: it was invariably present in >5% of UH cases and higher than for conventional PCa. Importantly, men with mucinous UH did not have worse pathology and no information was available for PIN-like PCa.

Second, almost all UHs had worse oncological outcomes in comparison to conventional PCa. Several series reported that UHs had not only lower BCR-free survival rates but also a higher likelihood of metastatic progression. Furthermore, cribriform/intraductal and cribriform UHs were associated with a higher risk of cancer-related death. Contrarily, mucinous and PIN-like UHs had similar outcomes compared to conventional PCa. In this context, a study focusing on PIN-like PCa did not observe any cases of BCR, suggesting excellent prognosis for this UH [33,51,58].

Third, our results mainly relate to patients treated with RP, since evidence on the impact of UH in men managed with RT is limited. Two of the five studies that included RT did not detail the numbers of patients with UHs, and the remaining three included results for only 89 men. This precluded comparison of patients with UHs managed with RP versus RT, despite the large body of literature showing equivalent oncological control of RT and RP for conventional PCa [60,61].

Fourth, registry-based studies confirmed a trend towards worse pathology and/or mortality for ductal and intraductal carcinoma and similar survival for mucinous UH in comparison to conventional PCa. Registries also provided information on additional subtypes, including signet ring cell, adenosquamous, and sarcomatoid UHs, as well as neuroendocrine tumors. All were associated with a trend towards poorer survival. It is likely that these UHs are underreported in institutional series owing to their relatively rare occurrence as primary disease. Their often more advanced stage at presentation [8] would exclude them from analysis in this systematic review, which focused on nonmetastatic PCa treated with curative intent.

From a clinical perspective, our findings suggest that not all PCa UHs are equal. In particular, intraductal, cribriform, and ductal UHs might be associated with worse features at final pathology and a higher risk of BCR, metastasis, and PCa-related death. These UHs may therefore be considered as high risk and patients should be counseled on the risk of worse oncological control associated with curative-intent therapies in this setting. Conversely, some UHs, namely mucinous and PIN-like PCa, do not seem to be more aggressive than conventional PCa and may therefore be con-

sidered as low-risk UHs. In addition, as for other diseases [62], clinicians should be aware of the existence of these distinct UHs, their classifications and their clinical implications. Finally, our results suggest that the presence of certain UHs (intraductal, cribriform, and ductal UH) at prostate biopsy should be considered as a criterion for exclusion from AS, while mucinous and PIN-like PCa should not.

From a research perspective, we highlighted several gaps in our understanding of UHs and their optimal management. Large prospective studies and comparison of different treatment strategies represent a research priority. Several types, subtypes, and patterns also lack any evidence at all and clinical outcomes should be urgently assessed. Molecular characterization of UHs and their inclusion in risk stratification models are also major points that should be addressed in the near future. Interestingly, UHs showing a higher risk of adverse outcomes were rarely associated with GG 1 PCa, while those at lower risk were more frequently diagnosed as GG 1 disease. This is in line with the 2019 ISUP consensus meeting on PCa grading, which recommended that any cribriform or intraductal carcinoma intermixed with otherwise GS 3 + 3 = 6 cancer in diagnostic biopsies should be accounted for in grading and thus be assigned a higher grade (eg, 97% Gleason pattern 3 intermixed with 3% intraductal would now be graded as GS 3 + 4 = 7 or GG 2). Possibly, pathological review of the cases at a higher risk associated with GG 1 should be carried out.

Importantly, evidence relies on low quality retrospective data. Several institutions published one or more paper based on the same series, possibly causing bias related to multiple data entry. Furthermore, pathological review, which is a cornerstone of UH-related studies, was not always performed. The series included in the review reported that conventional PCa was used as the comparator for UH. However, the absence of pathological review in some studies may have led to misclassification of some UHs within the conventional PCa group. Hence, the current work and knowledge on UH should be interpreted with caution. Nonetheless, we are the first to use a standardized a priori methodology and include an ad hoc review of the pathological criteria and definitions used in the series included. Although the latest WHO 2022 criteria were published after registration of our prospective protocol, pathological evaluation allowed us to update the results in compliance with the latest classification and terminology.

4. Conclusions

On the basis of retrospective evidence, mainly derived from RP series, some UHs, namely intraductal, cribriform, and ductal UHs, may be associated with worse pathological and oncological outcomes, while mucinous and PIN-like UH are not. PCa specialists should be aware of UHs, their classification, and their clinical implications.

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References

[1] World Health Organization. WHO classification of tumours; urinary and male genital tumours. ed. 5. Lyon, France: International Agency for Research on Cancer; 2022.
[2] Marcus DM, Rossi PJ, Goodman M, Jani AB, Osunkoya AO. A comprehensive review of incidence and survival in patients with rare histological variants of prostate cancer in the United States from 1973 to 2008. Prostate Cancer Prostat Dis 2012;15:283–8. https://doi.org/10.1038/pcan.2012.4.
[3] Miura N, Mori K, Mostafaei H, et al. The prognostic impact of intraductal carcinoma of the prostate: a systematic review and meta-analysis. J Urol 2020;204:909–17. https://doi.org/10.1097/JU.0000000000001290.
[4] Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs—part B: prostate and bladder tumours. Eur Urol 2016;70:106–19. https://doi.org/10.1016/j.eururo.2016.02.028.
[5] van Leenders GJLH, van der Kwast TH, Iczkowski KA. The 2019 International Society of Urological Pathology consensus conference on prostate cancer grading. Eur Urol 2020;44:87–99. https://doi.org/10.1016/j.eururo.2020.08.004.
[6] Epstein JI, Amin MB, Fine SW, et al. The 2019 Genitourinary Pathology Society (GUPS) white paper on contemporary grading of prostate cancer. Arch Pathol Lab Med 2021;145:461–93. https://doi.org/10.5858/arpa.2020-0015-ra.
[7] Tu X, Chang T, Nie L, et al. Large cell neuroendocrine carcinoma of the prostate: a systematic review and pooled analysis. Urol Int 2019;103:383–90. https://doi.org/10.1159/000499883.
[8] Parizi MK, Iwata T, Kimura S, et al. Focal neuroendocrine differentiation of conventional prostate adenocarcinoma as a prognostic factor after radical prostatectomy: a systematic review and meta-analysis. Int J Mol Sci 2019;20:1374. https://doi.org/10.3390/ijms20061374.
[9] Porter LH, Lawrence MG, Ilic D, et al. Systematic review links the prevalence of intraductal carcinoma of the prostate to prostate cancer risk categories. Eur Urol 2017;72:492–5. https://doi.org/10.1016/j.eururo.2017.03.013.
[10] Knoll T, Omar MI, MacLennan S, et al. Key steps in conducting systematic reviews for underpinning clinical practice guidelines: methodology of the European Association of Urology. Eur Urol 2018;73:290–300. https://doi.org/10.1016/j.eururo.2017.08.016.
[11] Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series. In: Better knowledge for better health. Abstracts of the 21st Cochrane Colloquium, 19–23 September 2013, Québec City, Canada. Chichester, UK: John Wiley & Sons; 2013.
[12] Marra G, Valerio M, Heidegger I, et al. Management of patients with node-positive prostate cancer at radical prostatectomy and pelvic lymph node dissection: a systematic review. Eur Urol Oncol 2020;3:565–81. https://doi.org/10.1016/j.euo.2020.08.005.
[13] Mitropoulos D, Artibani W, Graefen M, Remzi M, Rouprêt M, Truss M. Reporting and grading of complications after urologic surgical procedures: an ad hoc EAU Guidelines Panel assessment and recommendations. Eur Urol 2012;61:341–9. https://doi.org/10.1016/j.eururo.2011.10.033.
[14] Kweldam CF, Kümmerlin IP, Nieboer D, et al. Presence of invasive cribriform or intraductal growth at biopsy outperforms percentage grade 4 in predicting outcome of Gleason score 3+4=7 prostate cancer. Mod Pathol 2017;30:1126–32.
[15] Zhu S, Zhao J-G, Chen J-R, et al. Intraductal carcinoma of the prostate in prostate biopsy samples: correlation with aggressive pathological features after radical prostatectomy and prognostic value in high-risk prostate cancer. Asian J Androl 2020;22:519–25. https://doi.org/10.4103/aja.aja_117_19.
[16] Jang WS, Shin S-J, Yoon CY, et al. Prognostic significance of the proportion of ductal component in ductal adenocarcinoma of the prostate. J Urol 2017;197:1048–53. https://doi.org/10.1016/j.juro.2016.11.104.
[17] Kim A, Kwon T, You D, et al. Clinicopathological features of prostate ductal carcinoma: matching analysis and comparison with prostate acinar carcinoma. J Korean Med Sci 2015;30:385–9. https://doi.org/10.3346/jkms.2015.30.4.385.
[18] Jeong SU, Kekatpure AK, Hwang HS, et al. Diverse immunoprofile of ductal adenocarcinoma of the prostate with an emphasis on the prognostic factors. J Pathol Transl Med 2017;51:471–81. https://doi.org/10.4132/jptm.2017.06.02.
[19] Tan YG, Huang HH, Chen K, et al. Prostatic ductal adenocarcinoma variant predicts worse pathological and oncological outcomes: Insight from over 1000 consecutive patients from a large prospective uro-oncology registry. Prostate 2021;81:242–51. https://doi.org/10.1002/pros.24100.
[20] Miyai K, Divatia MK, Shen SS, Ayala AG, Ro JY, Miles BJ. 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.
[21] Hansum T, Hollemans E, Verhoef EI, et al. Comedonecrosis Gleason pattern 5 is associated with worse clinical outcome in operated prostate cancer patients. Mod Pathol 2021;34:2064–70. https://doi.org/10.1038/s41379-021-00860-4.
[22] Hollemans E, Verhoef EI, van Leenders GJLH, et al. Clinical outcome comparison of grade group 1 and grade group 2 prostate cancer with and without cribriform architecture at the time of radical prostatectomy. Histopathology 2020;76:755–62. https://doi.org/10.1111/his.14064.
[23] Kweldam CF, Kümmerlin IP, Nieboer D, et al. Prostate cancer outcomes of men with biopsy Gleason score 6 and 7 without cribriform or intraductal carcinoma. Eur J Cancer 2016;66:26–33. https://doi.org/10.1016/j.ejca.2016.07.012.
[24] Hollemans E, Verhoef EI, Bangma CH, et al. Cribriform architecture in radical prostatectomies predicts oncological outcome in Gleason

score 8 prostate cancer patients. Mod Pathol 2021;34:184–93. https://doi.org/10.1038/s41379-020-0625-x.
[25] Masoomian M, Downes MR, Sweet J, et al. Concordance of biopsy and prostatectomy diagnosis of intraductal and cribriform carcinoma in a prospectively collected data set. Histopathology 2019;74:474–82. https://doi.org/10.1111/his.13747.
[26] Kweldam CF, Van Leenders GJLH, Wildhagen MF, Bangma CH, Steyerberg EW, Van Der Kwast TH. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. Mod Pathol 2015;28:457–64. https://doi.org/10.1038/modpathol.2014.116.
[27] Efstathiou E, Abrahams NA, Tibbs RF, 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.
[28] Chow K, Harewood L, Peters JS, et al. Ductal variant prostate carcinoma is associated with a significantly shorter metastasis-free survival. Eur J Cancer 2021;148:440–50. https://doi.org/10.1016/j.ejca.2020.12.030.
[29] Harkin T, Elhage O, Chandra A, et al. High ductal proportion predicts biochemical recurrence in prostatic ductal adenocarcinoma. BJU Int 2019;124:907–9. https://doi.org/10.1111/bju.14831.
[30] Trinh VQ, Benzerdjeb N, Chagnon-Monarque S, et al. Retrospective study on the benefit of adjuvant radiotherapy in men with intraductal carcinoma of prostate. Radiat Oncol 2019;14:60. https://doi.org/10.1186/s13014-019-1267-3.
[31] Keefe DT, Breau RH, Morash C, et al. Cribriform morphology predicts upstaging after radical prostatectomy in patients with Gleason score 3 + 4 = 7 prostate cancer at transrectal ultrasound (TRUS)-guided needle biopsy. Virchows Arch 2015;467:437–42. https://doi.org/10.1007/s00428-015-1809-5.
[32] Samaratunga H, Duffy D, Yaxley J, Delahunt B. Any proportion of ductal adenocarcinoma in radical prostatectomy specimens predicts extraprostatic extension. Hum Pathol 2010;41:281–5. https://doi.org/10.1016/j.humpath.2009.08.010.
[33] Samaratunga H, Delahunt B, Srigley JR, et al. Mucinous adenocarcinoma of prostate and prostatic adenocarcinoma with mucinous components: a clinicopathological analysis of 143 cases. Histopathology 2017;71:641–7. https://doi.org/10.1111/his.13278.
[34] Vinceneux A, Fromont G, Bruyere F, et al. Ductal adenocarcinoma of the prostate: Clinical and biological profiles. Prostate 2017;77:1242–50. https://doi.org/10.1002/pros.23383.
[35] Trinh VQ, Sirois J, Benzerdjeb N, et al. The impact of intraductal carcinoma of the prostate on the site and timing of recurrence and cancer-specific survival. Prostate 2018;78:697–706. https://doi.org/10.1002/pros.23513.
[36] Downes MR, Xu B, van der Kwast TH. Cribriform architecture prostatic adenocarcinoma in needle biopsies is a strong independent predictor for lymph node metastases in radical prostatectomy. Eur J Cancer 2021;148:432–9. https://doi.org/10.1016/j.ejca.2020.09.016.
[37] Tonttila PP, Ahtikoski A, Kuisma M, Paakko E, Hirvikoski P, Vaarala MH. Multiparametric MRI prior to radical prostatectomy identifies intraductal and cribriform growth patterns in prostate cancer. BJU Int 2019;124:992–8. https://doi.org/10.1111/bju.14812.
[38] Hollemans E, Verhoef EI, van Leenders GJLH, et al. Prostate carcinoma grade and length but not cribriform architecture at positive surgical margins are predictive for biochemical recurrence after radical prostatectomy. Am J Surg Pathol 2020;44:191–7. https://doi.org/10.1097/PAS.0000000000001384.
[39] Trudel D, Downes MR, Kron KJ, Van Der Kwast TH, Sykes J, Trachtenberg J. Prognostic impact of intraductal carcinoma and large cribriform carcinoma architecture after prostatectomy in a contemporary cohort. Eur J Cancer 2014;50:1610–6. https://doi.org/10.1016/j.ejca.2014.03.009.
[40] Chua MLK, Lo W, Pintilie M, 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.
[41] Kweldam CF, Kummerlin IP, Verhoef EI, 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.
[42] O'Brien BA, Cohen RJ, Wheeler TM, Moorin RE. 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.
[43] Kato M, Majima T, Ishida S, 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.
[44] Van Der Kwast T, Al Daoud N, Collette L, 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.
[45] Kato M, Sano T, Majima T, et al. Response of intraductal carcinoma of the prostate to androgen deprivation therapy predicts prostate cancer prognosis in radical prostatectomy patients. Prostate 2020;80:284–90. https://doi.org/10.1002/pros.23942.
[46] Kato M, Majima T, Funahashi Y, et al. Prognostic parameter for high risk prostate cancer patients at initial presentation. Prostate 2018;78:11–6. https://doi.org/10.1002/pros.23438.
[47] Greenland NY, Cowan JE, Zhang L, et al. Expansile cribriform Gleason pattern 4 has histopathologic and molecular features of aggressiveness and greater risk of biochemical failure compared to glomerulation Gleason pattern 4. Prostate 2020;80:653–9. https://doi.org/10.1002/pros.23977.
[48] Leo P, Chandramouli S, Bera K, et al. Computationally derived cribriform area index from prostate cancer hematoxylin and eosin images is associated with biochemical recurrence following radical prostatectomy and is most prognostic in Gleason grade group 2. Eur Urol Focus 2021;7:722–32. https://doi.org/10.1016/j.euf.2021.04.016.
[49] Kir G, Sarbay BC, Topal CS, Gumus E. The association of the cribriform pattern with outcome for prostatic adenocarcinomas. Pathol Res Pract 2014;210:640–4. https://doi.org/10.1016/j.prp.2014.06.002.
[50] Choy B, Pearce SM, Anderson BB, et al. Prognostic significance of percentage and architectural types of contemporary Gleason pattern 4 prostate cancer in radical prostatectomy. Am J Surg Pathol 2016;40:1400–6. https://doi.org/10.1097/PAS.0000000000000691.
[51] Tavora F, Epstein JI. High-grade prostatic intraepithelial neoplasialike ductal adenocarcinoma of the prostate: a clinicopathologic study of 28 cases. Am J Surg Pathol 2008;32:1060–7. https://doi.org/10.1097/PAS.0b013e318160edaf.
[52] Packiam VT, Patel SG, Pariser JJ, et al. Contemporary population-based comparison of localized ductal adenocarcinoma and high-risk acinar adenocarcinoma of the prostate. Urology 2015;86:777–82. https://doi.org/10.1016/j.urology.2015.07.009.
[53] Bronkema C, Arora S, Keeley J, et al. Impact of treatment modality on overall survival in localized ductal prostate adenocarcinoma: a National Cancer Database analysis. Urol Oncol 2021;39:366. https://doi.org/10.1016/j.urolonc.2020.11.013.
[54] Weiner AB, Patel SG, Richards KA, Eggener SE, Szmulewitz RZ. Population-based analysis of treatment modalities and survival for clinically localized small-cell carcinoma of the prostate. Prostate Cancer Prostat Dis 2014;17:286–91. https://doi.org/10.1038/pcan.2014.26.
[55] Bronkema C, Arora S, Sood A, et al. Rare histological variants of prostate adenocarcinoma: a National Cancer Database analysis. J Urol 2020;204:260–5. https://doi.org/10.1097/JU.0000000000001011.
[56] Dinerman BF, Golan R, Bernstein AN, et al. Population-based study of the incidence and survival for intraductal carcinoma of the prostate. Urol Oncol 2017;35:673.e9–e14. https://doi.org/10.1016/j.urolonc.2017.08.015.
[57] Patel M, Bimali M, Howie C, et al. The role of radiotherapy among patients with prostate ductal adenocarcinoma. Clin Genitourin Cancer 2021;19:e41–50. https://doi.org/10.1016/j.clgc.2020.07.004.
[58] Osunkoya AO, Nielsen ME, Epstein JI. Prognosis of mucinous adenocarcinoma of the prostate treated by radical prostatectomy: a study of 47 cases. Am J Surg Pathol 2008;32:468–72. https://doi.org/10.1097/PAS.0b013e3181589f72.
[59] Karakoc S, Celik S, Bozkurt O, et al. Prognostic value of intraductal carcinoma for adjuvant radiotherapy candidates after radical prostatectomy. Int J Clin Pract 2021;75:e14099. https://doi.org/10.1111/ijcp.14099.
[60] Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer.

N Engl J Med 2016;375:1415–24. https://doi.org/10.1056/NEJMoa1606220.
[61] Wolff RF, Ryder S, Bossi A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. Eur J Cancer 2015;51:2345–67. https://doi.org/10.1016/j.ejca.2015.07.019.
[62] Moschini M, D'Andrea D, Korn S, et al. Characteristics and clinical significance of histological variants of bladder cancer. Nat Rev Urol 2017;14:651–68. https://doi.org/10.1038/nrurol.2017.125.
[63] Tu SM, Lopez A, Leibovici D, et al. Ductal adenocarcinoma of the prostate: clinical features and implications after local therapy. Cancer 2009;115:2872–80. https://doi.org/10.1002/cncr.24326.
[64] Patil PA, McKenney JK, Reynolds JP, Przybycin CG, Magi-Galluzzi C. Clinical significance and EZH2, ERG and SPINK1 protein expression in pure and mixed ductal adenocarcinoma of the prostate. Histol Histopathol 2019;34:381–90. https://doi.org/10.14670/HH-18-046.