

Review

# Intraductal Carcinoma of the Prostate as a Cause of Prostate Cancer Metastasis: A Molecular Portrait

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**Simple Summary:** Most men with prostate cancer will live as long as those who do not have prostate cancer. However, some men will die early of their disease due to a particular type of prostate cancer associated with recurrence and metastasis: intraductal carcinoma of the prostate. In this review, we discuss the associations between intraductal carcinoma of the prostate and metastasis, and the contemporary knowledge about the molecular alterations of intraductal carcinoma of the prostate.



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**Abstract:** Intraductal carcinoma of the prostate (IDC-P) is one of the most aggressive types of prostate cancer (PCa). IDC-P is identified in approximately 20% of PCa patients and is associated with recurrence, metastasis, and PCa-specific death. The main feature of this histological variant is the colonization of benign glands by PCa cells. Although IDC-P is a well-recognized independent parameter for metastasis, mechanisms by which IDC-P cells can spread and colonize other tissues are not fully known. In this review, we discuss the molecular portraits of IDC-P determined by immunohistochemistry and genomic approaches and highlight the areas in which more research is needed.

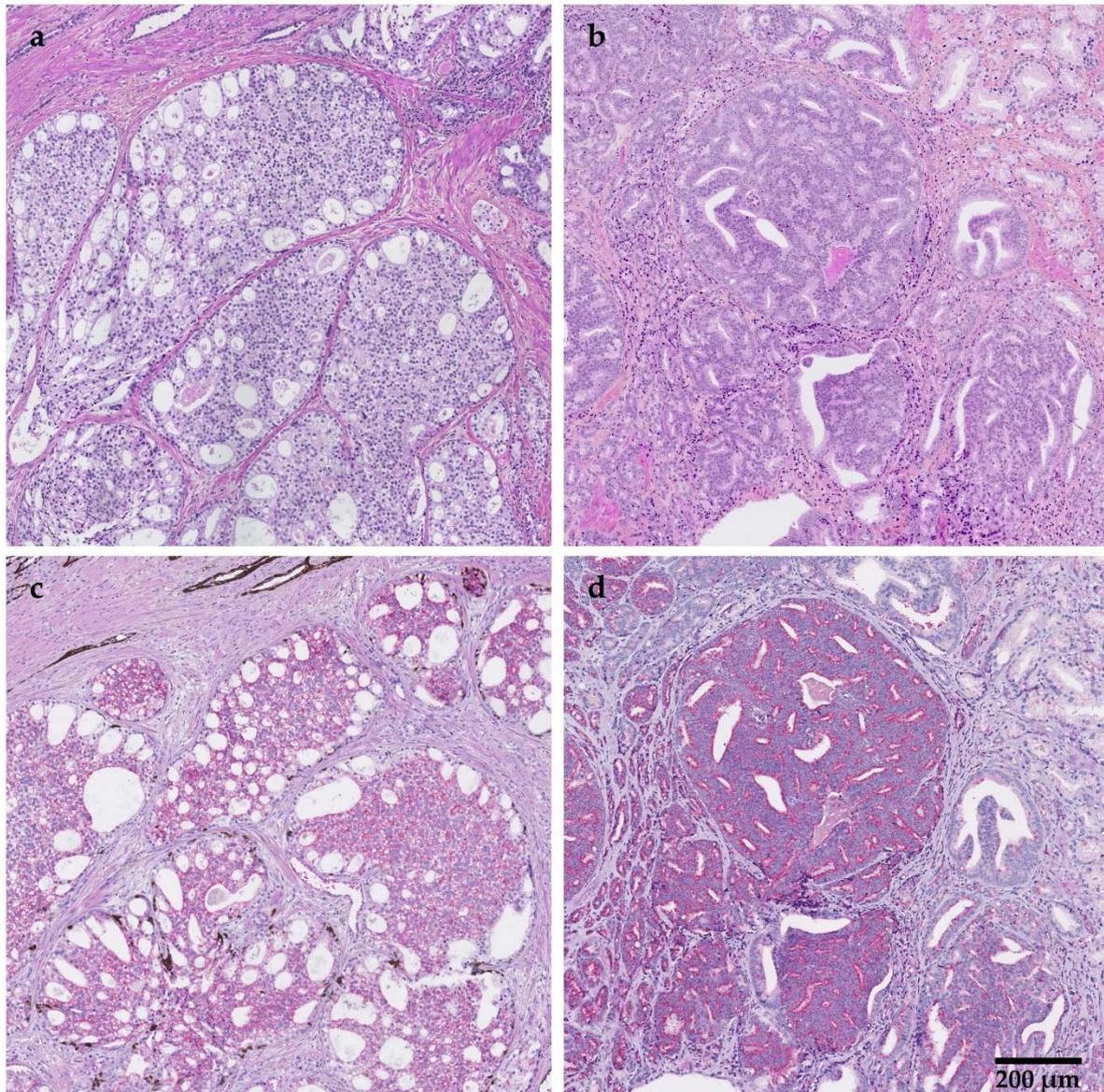
**Keywords:** intraductal carcinoma of the prostate (IDC-P); metastasis; biomarkers; immunohistochemistry; genomic; Raman micro-spectroscopy

## 1. Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer of men, accounting for 26% of all malignancies found in North American men, and the second cause of cancer-related death [1]. When PCa is localized, the 5-year survival rate of patients is nearly 100%; yet when PCa has metastasized, the 5-year survival rate steeply declines to 28% despite intensive therapy [2,3]. Many factors are associated with survival in PCa, such as tumour stage and tumour grade. In PCa, the tumour grade is evaluated according to how glands are well formed (pattern 3), unrecognizable (pattern 5) or in between (pattern 4), and added together according to their relative abundance to generate the Gleason score (6 to 10) which is then transformed to grade groups (1 to 5) [4].

Among the factors influencing PCa survival is intraductal carcinoma of the prostate (IDC-P), a growth of malignant cells found in benign prostatic ducts and acini (Figure 1a,c), recently recognized as a distinct aggressive variant of PCa [5–7]. IDC-P is identified

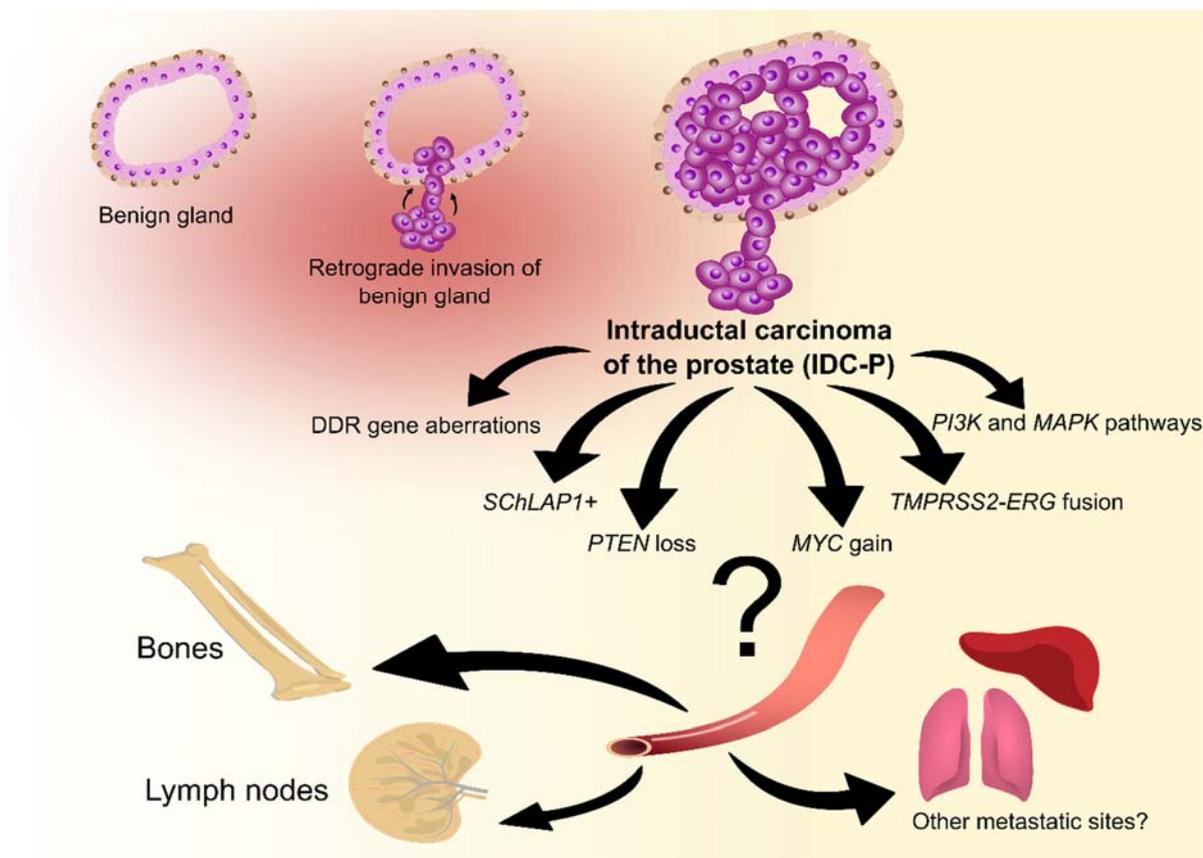
in approximately 20% of radical prostatectomies (RPs), often with invasive high-grade, high-risk PCa, and has been associated with early biochemical recurrence, metastasis, castration-resistant prostate cancer (CRPC) and poor survival [8]. Of note, despite similar nomenclature and associations with poor outcomes, IDC-P is morphologically distinct from ductal adenocarcinoma [9]. Briefly, ductal adenocarcinoma is most often directly in contact with the stroma (i.e., is not within a benign duct or acini), and is recognized by columnar pseudostratified epithelium with elongated nuclei [9]. Thus, the two entities should not be confused.



**Figure 1.** Intraductal carcinoma of the prostate (IDC-P) (a,c) and cribriform type pattern 4 prostate cancer (CC) (b,d). Hematoxylin phloxine saffron staining (a,b) or immunostaining for high molecular weight cytokeratins and p63 (basal cell markers, brown) and  $\alpha$ -methylacyl-CoA racemase (prostate cancer marker, red) with hematoxylin and eosin counterstaining (c,d), highlighting the basal cells surrounding IDC-P and the direct contact between CC and the tumour stroma. Scale bar: 200  $\mu$ m.

Although the diagnostic criteria and the clinical significance of IDC-P have become clearer since its first description by Kovi et al. in 1985 [7], response to standard treatment is better known, but specific treatment options have yet to be established [10–18]. Of all

the adverse features associated with IDC-P, metastatic disease is the most threatening to the patient. IDC-P has been associated with lymph node metastasis [19–25], distant metastasis [26–35], poor outcome in men with metastatic disease and CRPC [17,18,36–40], PCa-specific death and poor overall survival [25,27,31,36,39–43]. Understanding the molecular cascades underlying the invasion of PCa cells into benign ducts, and their escape from the prostate and from androgen dependency, would help discover biomarkers of aggressive disease and the development of much-needed targeted therapies. Here, we review the associations between IDC-P and metastatic PCa, the current knowledge about treatment response of IDC-P and align these associations with the known molecular alterations of IDC-P (Figure 2) while highlighting areas that could benefit from further investigations.



**Figure 2.** Known molecular alterations for the pathogenesis and progression of intraductal carcinoma of the prostate (IDC-P). DDR: DNA-damage repair; *SchLAP1*: second chromosome locus associated with prostate cancer-1; *PTEN*: phosphatase and tensin homolog; *ERG*: ETS-related gene; PI3K: phosphoinositide 3-kinase; *MAPK*: mitogen-activated protein kinase.

## 2. IDC-P Is an Independent Parameter for Metastasis and Survival

### 2.1. IDC-P Predicts the Presence of Lymph Node Metastasis at Diagnosis

Lymph node metastasis is associated with shorter disease-free survival in PCa [44]. IDC-P has been frequently associated with lymph node metastasis [19–25] (summarized in Supplemental Table S1A), with a hazard ratio (HR) of 3.79 to develop lymph node-positive disease, as described in a recent meta-analysis [13]. The first report of this association by O’Brien et al. [19] evaluated the predictive impact of IDC-P in 50 high-risk PCa patients treated with neoadjuvant chemotherapy. Interestingly, only IDC-P (multivariate odds ratio (OR) of 4.6, 95% confidence interval (CI) of 1.5–14.2,  $p = 0.007$ ) could predict the presence of lymph node metastases [19].

In treatment-naïve cohorts, Xu et al. [20] first showed in 316 men with clinically localized, bilateral PCas without metastasis (cT2N0M0) who underwent RP, that IDC-P

was associated, but not independently, with lymph node metastasis. Kryvenko et al. [21] compared the clinicopathological characteristics between patients with Gleason score 7 Pca who had lymph node metastases and those without any other metastasis at RP. Of the 368 RP specimens, 184 patients had metastases to lymph nodes, and these patients were significantly more likely to have IDC-P (78/184) than patients that did not have any metastases (38/184) (42.4% vs. 20.7%,  $p < 0.001$ ) [21].

In two retrospective studies in treatment-naïve men, Downes and colleagues [22,23] evaluated IDC-P in conjunction with cribriform type pattern 4 (CC) as a predictive parameter in detecting lymph node metastases. CC is an adverse histopathological feature of the prostate that is now classified as a Gleason pattern 4, and IDC-P and CC are often assessed together due to the difficulty in correctly distinguishing the two histopathologies [45–49] (Figure 1b,d). Accordingly, Downes et al. [22] examined IDC-P and CC together and showed that IDC-P/CC histopathology was present in 94% of all RP specimens from 110 node-positive patients. Although there was no association between the grade at RP and the nodal grade, the grade assigned to the largest node was associated with shorter survival [22]. Downes et al. [23] then evaluated the role of IDC-P/CC in 543 patients who underwent RP, of which 275 patients had matched biopsies. IDC-P/CC was significantly associated with lymph node metastases in the RP and biopsy cohort (multivariate OR: 5.12, 95% CI: 1.37–19.2,  $p = 0.015$ ; and multivariate OR: 4.42, 95% CI: 1.29–15.14,  $p = 0.018$ , respectively) [23].

Both very small and large-scale studies point to the same associations. Lindberg et al. [24] published a case study in which the DNA alterations in the prostatic ducts colonized by IDC-P shared 83% of the break-point regions with lymph node metastases, directly implicating regional metastatic PCa as an outcome of IDC-P [24]. On the other hand, Dinerman et al. [25] performed a Surveillance, Epidemiology and End Results Program (SEER) retrospective study in which IDC-P alone had predictive value on lymph node metastases in 242 out of 159,777 RP specimens (5.8% vs. 2.4% when IDC-P is absent,  $p < 0.001$ ) [25].

These studies [13,19–25,31] establish that the presence of IDC-P/CC is strongly associated with lymph node metastasis at diagnosis. However, the only available studies in treatment-naïve men of all grades have been conducted by merging IDC-P with CC. As IDC-P is likely resistant to neoadjuvant therapy with either hormone therapy or chemotherapy [16,19,50–52], the role of IDC-P alone as a predictor of lymph node metastasis in patients with higher grade PCa should be better clarified. Interestingly, Hollemans et al. studied 408 men with NOM0 grade group 2 PCas, and observed that the occurrence of lymph node metastasis was not statistically different when comparing men with CC and IDC-P and men with IDC-P alone [53].

## 2.2. IDC-P Predicts the Occurrence of Distant Metastasis

In addition to N1 disease, IDC-P has been often associated with distant metastasis [26–35] (summarized in Supplemental Table S1B). When comparing 85 men who experienced recurrence detected either by biopsy or radiology, Trinh et al. [26] showed that men with IDC-P at RP developed distant metastasis more frequently than loco-regional recurrence (OR: 6.27, 95% CI: 1.43–27.6,  $p = 0.015$ ). In 206 high-risk PCas, Kimura et al. [31] showed that IDC-P status was significantly correlated with progression-free survival (multivariate HR: 3.07, 95% CI: 1.44–6.58,  $p = 0.0038$ ), which was defined as time from RP to development of local or distant metastases.

In 2019, Tom et al. [27] evaluated the clinical outcomes of IDC-P positive patients and demonstrated that IDC-P was an adverse prognostic parameter of distant metastasis in a cohort of 237 patients with Gleason score 7 Pca treated with external beam radiotherapy. In this cohort, CC was not significantly associated with distant metastasis-free survival unless it was evaluated in conjunction with IDC-P (multivariate HR: 4.18, 95% CI: 1.43–12.28,  $p = 0.01$ ), and IDC-P was not identified without CC in the biopsies [27]. Similarly, van der Kwast et al. [28] studied two cohorts of men with PCas treated by radiation therapy: one including men with intermediate-risk PCas and the other including men with high-

risk PCas who were part of a clinical trial evaluating the addition of long-term androgen deprivation therapy to radiation therapy. In this study, IDC-P was associated with shorter time to clinical progression (local, distant or death), when men were treated by radiation therapy only (multivariate HR: 2.33, 95% CI: 1.14–4.76,  $p = 0.02$ ), but only in univariate analysis when men were exposed to androgen deprivation therapy (HR: 2.83, 95% CI: 1.16–6.92,  $p = 0.018$ ) [28].

In an earlier case-control study including 161 men with Gleason score 7 PCas (52 with metastases, disease-specific mortality or both), Kweldam et al. [29] showed that IDC-P was a univariate predictor for distant metastasis. In their study, IDC-P was strongly associated with CC ( $p < 0.001$ ), and both CC and IDC-P were adverse predictors for distant metastasis-free survival. However, IDC-P lost significance in multivariate analyses (multivariate HR for CC: 8.0, 95% CI: 3.0–21,  $p < 0.001$ ; univariate HR for IDC-P: 2.5, 95% CI: 1.2–4.7,  $p = 0.007$ ) [29]. It is worth noting that if CC is highly correlated with IDC-P, including these two factors in a multivariate model may bias the final model.

Other groups have implicated IDC-P/CC together as a predictor of the development of distant metastases [30,32–34] in PCa patients. In 2017, Chua et al. [30] evaluated 1325 men treated for localized PCa, and found that patients with IDC-P/CC had an increased likelihood of developing distant metastasis (multivariate HR: 3.31, 95% CI: 1.76–6.21,  $p < 0.001$ ) [30]. In 2019, Hollemans et al. evaluated the impact of IDC-P/CC in 1064 first-line RPs and found that IDC-P/CC predicted shorter metastasis-free survival (multivariate HR: 9.9, 95% CI: 3.9–25.5,  $p < 0.001$ ) [32]. Subgroup analyses showed the same results in the 140 Gleason score 8 RP specimens [33] and in the 854 grade group 1 and 2 RP specimens, although metastases were infrequent in this group [34]. The very few patients who developed distant metastasis (6%) harboured IDC-P/CC in their RPs [34].

Lastly, Isaacsson Velho et al. [35] studied the occurrence of metastasis in 60 men with primary Gleason pattern 5 at RP, of which nine (15%) showed either ductal or intraductal histology. In these men, IDC-P and/or ductal adenocarcinoma were associated with shorter metastasis-free survival (multivariate HR: 3.78, 95% CI: 1.51–9.45,  $p = 0.004$ ) [35].

Globally, regardless of the risk stratification or whether PCa was treated by RP or radiation therapy, IDC-P alone or in combination with CC or ductal adenocarcinoma has been associated with the development of distant metastasis [26–35]. Interestingly, only Kweldam et al. [29] compared the impact of IDC-P and CC alone and in combination. However, their important study included only Gleason score 7 PCas.

### 2.3. IDC-P Predicts Poor Prognosis in Men with Metastatic PCa

Many groups have assessed the clinical impact of IDC-P in men with metastatic PCas on first diagnosis [17,18,36–40] (summarized in Supplemental Table S1C). One of these groups, led by Zeng, initially verified the time to CRPC in men diagnosed with metastatic disease and IDC-P [36]. Time to CRPC was cut in half when IDC-P was present in the diagnostic biopsy (23 months vs. 46 months, multivariate HR: 4.89, 95% CI: 1.44–16.56,  $p = 0.011$ ). In a second study, Chen et al. [17] evaluated 45 patients initially diagnosed with bone metastatic PCas, which later progressed to CRPC. All patients were subjected to two transperineal prostate biopsies: one at the time of initial diagnosis and a second upon diagnosis of metastatic CRPC. As the prevalence of IDC-P increased from 20% to 62.5% between the two biopsies, IDC-P was associated with shorter time to prostate-specific antigen (PSA) doubling only when taking into account the second biopsy [17]. In another study with the same two-biopsy design, the prevalence of IDC-P increased from 28% to 47% at the time of CRPC, and IDC-P was associated with shorter overall survival (multivariate HR: 1.91, 95% CI 1.11–3.29,  $p = 0.020$ ) [37]. A high amount of IDC-P (>10% of the tumour content) was also associated with shorter CRPC-free survival (multivariate HR: 2.11, 95% CI: 1.52–2.93,  $p < 0.001$ ), and shorter overall survival (multivariate HR: 2.31, 95% CI: 1.38–3.87,  $p = 0.002$ ) in 644 de novo metastatic PCas [38]. Similarly, the same group identified IDC-P as an independent predictor of CRPC-free survival (HR: 1.82, 95% CI: 1.35–2.44,  $p < 0.001$ ) [39].

Other groups also studied the impact of IDC-P in men with de novo metastatic PCa. Kato et al. found that IDC-P was associated with cancer-specific survival (univariate HR: 2.13, 95% CI: 1.14–3.99,  $p = 0.0181$ ) and overall survival (multivariate HR: 2.66, 95% CI: 1.47–4.79,  $p = 0.0012$ ) in a cohort of 150 men with bone metastases at their initial PCa diagnosis [40]. Recently, Abascal-Junquera et al. [18] demonstrated the importance of IDC-P in 118 metastatic CRPC patients as they observed that the time to CRPC was shorter for the 37 men with IDC-P than for the 81 men without IDC-P (10 months vs. 25 months,  $p = 0.007$ ). Furthermore, time to second-line therapy with abiraterone or enzalutamide was also shorter for men with IDC-P (11 months vs. 6 months,  $p = 0.05$ ).

In contrast, Porter and al. [16] assessed overall survival in a small-scale study including 38 men who developed metastases after their initial diagnosis and found no significant difference in survival between men with and without IDC-P at diagnosis, despite a median follow-up of 4.9 years from diagnosis to CRPC [16].

Interestingly, most of these studies [17,18,36–40] establish IDC-P alone, without evaluating the impact of CC, as a prognostic factor in men diagnosed with de novo metastatic PCa to the bones and who progressed to CRPC. It should also be noted that all these studies excluded men with visceral metastases, which, although rare in PCa, could be associated differently with IDC-P.

#### 2.4. IDC-P Predicts Death from PCa

The association of IDC-P and poor outcome when diagnosed in M1 PCa is expectedly followed by an association of IDC-P with poor disease-specific survival and overall survival [13,25,27,31,36–43,54] (summarized in Supplemental Table S1D). The effect of IDC-P alone on disease-specific survival has been evaluated in the SEER database [25] in men with localized PCas [43] and in high-risk PCas [31,42]. IDC-P was significantly associated with shorter disease-specific survival in all studies [13,25,27,31,36–43,54] but one [42], with HRs varying from 1.7 to 4.48. Moreover, the association between IDC-P and overall survival has been evaluated in men with de novo metastatic disease (restricted to bone metastases) [36,38–40], CRPC [37] and in one cohort of high-risk patients [42], with HRs varying from 1.61 to 2.66. These results are consistent in a recent multivariate analysis [13].

Three studies addressed the combined impact of IDC-P and CC on disease-specific survival [27,29,54]. The first study [29] was the case-control study of men with metastases and/or lethal PCas by Kweldam et al. discussed above, in which IDC-P was associated with distant metastasis only in univariate analysis. Only CC was associated with PCa disease-specific survival (multivariate HR: 5.4, 95% CI: 2.0–15,  $p = 0.001$ ) [29]. The second study included men with Gleason score 7 PCas treated by external beam radiation therapy, and showed that CC alone was not associated with the occurrence of metastasis, but IDC-P combined with CC was associated with metastasis and disease-specific survival (multivariate HR: 14.26, 95% CI: 2.75–74.04,  $p = 0.0016$ ) [27]. Interestingly, in this cohort, IDC-P was not found without CC [27]. In the third study, the effect of IDC-P/CC on overall survival was compared to the effect of non-CC Gleason pattern 4 in the Health Professionals Follow-up Study and the Physicians' Health Study [54]. The presence of IDC-P/CC was evaluated on tissue microarrays of 0.6 mm-cores built from the primary PCa nodule or the nodule with the highest grade. Elfandy et al. showed that IDC-P/CC was associated with lethal disease (IDC-P/CC: 43/218 lethal cases, non-CC Gleason 4 pattern: 46/600 lethal cases; unadjusted HR: 2.66, 95% CI: 1.75–4.03), but the association lost statistical significance with adjustment for Gleason score, age, body-mass index and cTNM (full model HR: 1.45, 95% CI: 0.92–2.27).

Lastly, in the European Randomized study of Screening for Prostate Cancer (Rotterdam cohort), the incidence of IDC-P/CC in biopsy specimens of 15 men who died of PCa despite having cT1/2 disease with classical Gleason score  $\leq 6$  were compared to biopsy specimens of 64 men with non-fatal PCas and classical Gleason score  $\leq 6$ . After reclassification following the International Society of Urological Pathology (ISUP) 2014 modified Gleason

score, 63% (5/8) of men with grade group two fatal PCas had IDC-P/CC, compared to 13% (2/16) of men with non-fatal, grade group 2 PCas [55].

### 3. Treatment Response

Understanding how IDC-P responds to standard PCa treatment is crucial for the design of new targeted therapies. These questions have mostly been addressed in retrospective studies or in clinical trials with IDC-P as a secondary endpoint [15,17,19,37,50–52,56–59] (summarized in Supplemental Table S2). Currently, two ongoing studies in China focus on IDC-P treatment. One evaluates neoadjuvant androgen-deprivation therapy and abiraterone in IDC-P, and the other evaluates docetaxel and abiraterone in mCRPC and IDC-P. In addition, two other registered studies will be evaluating the presence of IDC-P or CC after neoadjuvant therapy as a secondary endpoint, and another will be evaluating the difference in time-to-recurrence according to IDC-P status as a secondary endpoint after radiation therapy with or without androgen-deprivation therapy. With the growing importance of IDC-P in PCa outcomes, more clinical trials are expected to focus on the treatment of IDC-P.

#### 3.1. Response to Neoadjuvant Chemotherapy, Androgen-Deprivation Therapy and Androgen Receptor Axis-Targeted Therapy

The first studies addressing the response to therapy of IDC-P were conducted in the neoadjuvant context in retrospective studies. Efstathiou et al. published [50] a study of 115 men who underwent RP after androgen ablation, alone or in combination with chemotherapy. This series included mostly men with high-grade disease (71% of Gleason score 8–10), and IDC-P/CC were present in 72% of RPs. In multivariate analysis, the presence of IDC-P/CC, margin status and treatment predicted biochemical recurrence (relative risk [RR] for IDC-P/CC: 2.98, standard error: 0.46,  $p = 0.02$ ) [50]. Similarly, O'Brien et al. [19] identified IDC-P in 20% of 50 RPs from men treated with neoadjuvant docetaxel and mitoxantrone for high-risk PCa and linked the presence of IDC-P and CC with shorter time to recurrence (multivariate HR: 2.6, 95%CI: 1.5–4.3,  $p < 0.001$  and multivariate HR: 2.3, 95%CI: 1.3–4.0,  $p = 0.003$ , respectively). In a cohort of men with high-risk PCa treated with neoadjuvant androgen-deprivation therapy, men with IDC-P found at both needle biopsy and RP were also shown to have shorter overall survival than men without IDC-P at needle biopsy (regardless of IDC-P status at RP) or men with IDC-P at needle biopsy but not on RP (multivariate HR: 3.2, 95%CI: 1.47–6.95,  $p = 0.0034$ ) [51].

The presence of IDC-P as a factor of response to neoadjuvant therapy has also been evaluated in post-hoc analysis of clinical trials or as secondary endpoints [52,56,57]. In a pooled analysis of three clinical trials evaluating neoadjuvant abiraterone and/or enzalutamide (androgen receptor axis-targeted therapy) in high-risk and unfavorable intermediate-risk patients, McKay et al. [56] showed that IDC-P was associated with a lack of exceptional pathological response at RP ( $n = 45$ , 0% vs. 41.7%,  $p = 0.001$ ) and with a lower rate of biochemical-free survival at three years (28% vs. 70%,  $p = 0.004$ ). In the histologic and genomic analyses of RPs from 37 men enrolled in a clinical trial of neoadjuvant androgen-deprivation therapy with enzalutamide [57], IDC-P and nuclear ERG expression were associated with incomplete or nonresponsive cases (univariate analyses,  $p = 0.013$  and  $p = 0.002$ , respectively) but CC was not. Based on a combination of IDC-P and ERG expression with deletion of >50% of chromosome 10 q and loss-of-function or hotspot alterations to *TP53*, a model was constructed to predict complete response after neoadjuvant treatment. This model classified 30/37 cases correctly (area under the curve: 0.89,  $p < 0.0001$ ) [57]. In a trial comparing abiraterone, leuprolide and prednisone with or without apalutamide, as there was no significant difference between treatment arms, IDC-P was associated with higher pathologic T stage (tumour extension), larger residual tumours, increased tumour cellularity and higher residual cancer burden [52].

### 3.2. Response to Chemotherapy or Androgen Receptor Axis-Targeted Therapy

In a study by Chen et al. [17], response to treatment was evaluated in 24 men who were initially diagnosed with bone metastatic PCa before progression to CRPC and who were treated with docetaxel-based chemotherapy. In this cohort, 6/9 men without IDC-P (67%) showed response to chemotherapy while only 3/15 with IDC-P (20%) responded to chemotherapy. The same group compared response to CRPC therapy according to IDC-P status at biopsy (at the time of metastatic CRPC) in a cohort of 96 men [37]. In men without IDC-P, response rates to docetaxel or abiraterone were similar (56% vs. 57%,  $p = 0.70$ ), whereas men with IDC-P showed similar response rates to abiraterone (52%) with only a 22% response rate in the docetaxel group [37].

In 2018, Yamamoto et al. [58] came to the same conclusion after studying a cohort of 79 men diagnosed with metastatic PCa who progressed to mCRPC without local treatment. As all men from this cohort were treated by androgen-deprivation therapy, men who received docetaxel had shorter median survival when their PCa harboured IDC-P (20.5 months vs. 53.2 months, HR: 2.98, 95%CI: 1.02–8.64,  $p = 0.044$ ) [58]. While men who received docetaxel had shorter survival with IDC-P than without IDC-P, men with IDC-P still fared better when they received chemotherapy with a median cancer-specific survival of 14.7 months without chemotherapy (median 20.5 months with chemotherapy, HR: 0.44, 95%CI: 0.22–0.91,  $p = 0.026$ ) [58]. Two years later, the same group compared the response to chemotherapy to the response to abiraterone or enzalutamide in a propensity score matching study including 170 men with CRPC [59]. In each treatment group, IDC-P was associated with shorter overall survival, which was not statistically significant in the abiraterone/enzalutamide group (HR for docetaxel group: 3.08, 95%CI 1.76–5.41,  $p < 0.001$ ; HR for abiraterone/enzalutamide group: 1.63, 95%CI: 0.77–3.47,  $p = 0.19$ ). However, patients with IDC-P did better when they received either abiraterone or enzalutamide compared to docetaxel (HR: 0.48, 95%CI: 0.26–0.86,  $p = 0.01$ ) [59].

### 3.3. Response to Adjuvant Radiation Therapy

Until now, only one study has evaluated the addition of radiation therapy to RPs when IDC-P is present [15]. In this study, the outcomes of 293 men with localized to locally advanced PCa were compared in function of the presence of high-risk factors (grade group 4–5, positive margins, extraprostatic extension or seminal vesicle invasion), which can be treated with adjuvant radiation therapy, and in function of the presence of IDC-P. Globally, men with IDC-P and no high-risk factors had a similar outcome than men without IDC-P but with at least one high-risk factor. In a multivariate analysis for the prediction of biochemical recurrence after RP, IDC-P was associated with shorter time to recurrence (HR: 2.39, 95%CI: 1.44–3.97,  $p = 0.001$ ) and adjuvant radiation therapy protected the men from recurrence (HR: 0.38, 95%CI: 0.17–0.85,  $p = 0.018$ ) [15].

## 4. Molecular Markers of IDC-P

To date, evidence has shown that IDC-P alone or in combination with CC is of tremendous importance to PCa outcome. Understanding the molecular characteristics of IDC-P is crucial for the identification and development of early detection tools and targeted therapies. Our knowledge of IDC-P has grown exponentially since a study in 2000 [60] that first detailed some molecular features of IDC-P in 26 patients, with expression of PSA (specific to prostate tissue), MIB-1 (a proliferation marker) and MUC2 (staining intestinal goblet-cell mucus) mostly in the central area of the proliferation, and androgen receptors (AR) expression mostly at its periphery. Here we describe the known molecular alterations of IDC-P compared to other components of prostatic tissue and PCa, as well as the prognostic impact of the molecular alterations associated with IDC-P.

### 4.1. IDC-P without Associated Invasive Carcinoma

Very few reports of isolated IDC-P have been published [61,62]. Khani et al. characterized four isolated IDC-P cases (three were entirely submitted for histology) as well as

11 cases in which IDC-P was identified in association with low grade (Gleason score 6) PCas [63] (Table 1). From seven sequenced IDC-P lesions (one with isolated IDC-P), four showed activating oncogenic driver mutations involving the *MAPK* and *PI3K* pathways, which are rarely involved in PCa but which are found with high frequency in ductal adenocarcinoma [64]. Moreover, these tumours showed less copy number alterations (CNAs) and a lower percentage of genome alterations. Other identified alterations included phosphatase and tensin homolog (*PTEN*) loss, *CHEK2* and *BRCA2* (DNA-damage repair [DDR] genes) mutations, *CDKN2A*, *RB1* and *CCND1* (cell cycle genes) mutations, along with other PCa-related alterations such as *MYC* amplification in four cases. Immunohistochemistry (IHC) showed low ETS-related gene (ERG) positivity prevalence (1/15), with partial or complete loss of *PTEN* in roughly half the cases (7/15), and 56% of discordance for the nine cases with sufficient tissue to evaluate adjacent invasive carcinoma.

**Table 1.** Overview of the study [63] describing IDC-P without associated invasive carcinoma in radical prostatectomies.

Method	Type of Alteration	Gene or Chromosome	Mutation/ Alteration	% Positivity (n/n)
NGS	Activating SNV (PI3K/MAPK pathways)	<i>PIK3CA</i> <i>AKT1</i> <i>MAP2K1</i> <i>KRAS</i> <i>BRAF</i>	p.H1047R p.E17K p.I99_K104del p.G13P p.K601E	57% (4/7)
	Other SNV	<i>PTEN</i>	Splicing	14% (1/7)
GW CNA analysis	CNA	<i>PTEN</i>	Loss	29% (2/7)
IHC	Protein loss	<i>PTEN</i>	–	47% (7/15)
NGS	Other SNV (DNA repair genes)	<i>BRCA2</i> <i>CDK12</i> <i>CHEK2</i>	p.L1740 * p.K756Q, p.K504 * p.I157T	29% (2/7)
	Other SNV	<i>FOXA1</i>	p.F266V p.F396 *	29% (2/7)
	Other SNV	<i>SPOP</i>	p.F133V	14% (1/7)
GW CNA analysis	CNA	<i>CDKN2A</i> <i>RB1</i> <i>CCND1</i>	Loss Loss Gain	71% (5/7)
	CNA	<i>MYC</i>	Gain	57% (4/7)
	CNA	<i>TP53</i>	Loss	14% (1/7)
	CNA	<i>CHD1</i>	Loss	14% (1/7)
	CNA	<i>TSC2</i>	Gain	14% (1/7)
	CNA	Chr. 8 (8p)	LOH	43% (3/7)
IHC	Protein overexpression	ERG	–	7% (1/15)

Abbreviations: CNA: copy number alteration; GW: Genome-wide; IHC: immunohistochemistry; LOH: loss of heterozygosity; NGS: next-generation sequencing; SNV: single-nucleotide variant.

#### 4.2. IDC-P Compared to High-Grade Intraepithelial Neoplasia (HGPIN) and to Adjacent Invasive Carcinoma

The prostatic ducts can be occupied by many lesions such as high-grade intraepithelial neoplasia (HGPIN), the presumed precursor of PCa, as well as clear cell cribriform hyperplasia and urothelial carcinoma [12]. IDC-P and HGPIN are on a spectrum of cellular atypia, and HGPIN is less atypical than IDC-P. Many studies have attempted to distinguish IDC-P from HGPIN and from lesions with intermediate characteristics, coined “atypical intraductal proliferation” (AIP) [65–69]. Logically, IDC-P has also been compared to adjacent invasive carcinoma. Altogether, the following studies largely demonstrated that IDC-P was

distinct from HGPIN but similar to AIP and adjacent invasive carcinoma, at least in terms of ERG and PTEN expression (summarized in Table 2). However, studies comparing IDC-P to HGPIN and adjacent invasive carcinoma using other markers or techniques, such as laser microdissection or spatial transcriptomics, are needed to complete our understanding of the relationships between PCa, IDC and HGPIN.

**Table 2.** Overview of the studies comparing IDC-P to high-grade intraepithelial neoplasia and to adjacent invasive carcinoma. Only IDC-P results are presented.

Specimen Type	Method	% Positivity (n/n)	Ref.
<i>TMPRSS2:ERG</i> fusion			
RP	Sanger sequencing	100% (4/4)	[70]
RP	FISH	94% (82/87)	[71]
RP	FISH (break-apart probe)	75% (36/48)	[72]
<i>PTEN</i> loss			
RP	Sanger sequencing	75% (3/4)	[70]
RP	Microsatellite analysis: <i>PTEN</i> (10q23) LOH	48% (13/27)	[73]
ERG protein overexpression			
RP	IHC	63% (20/32)	[74]
RP	IHC	61% (28/46)	[69]
RP	IHC	58% (26/45)	[66]
Bx	IHC	58% (29/50)	[67]
Bx	IHC	55% (33/60)	[68]
15 Bx; 8 RP; 6 TURP; 2 RCP	IHC	35% (11/31)	[75]
Bx	IHC	10% (12/128)	[76]
PTEN protein loss			
RP	IHC	89% (32/36)	[77]
RP	IHC	84% (38/45)	[66]
Bx	IHC	76% (38/50)	[67]
RP	IHC	75% (18/24)	[69]
Bx	IHC	75% (61/81)	[78]
Bx	IHC	72% (43/60)	[68]
RP	IHC	72% (23/32)	[74]
Other			
RP	CGH: −1q23 → q32, −5p, −6cen → q22, +7p, +7q, −8p, +8q21.1 → qter, −10p, −10q, −10q21 → qter, −13q, −13q14 → qter, −16q, −16q13 → qter, −17p, −18q, +19p, +19q	73% (8/11)	[73]
RP	Microsatellite analysis: <i>TP53</i> (17p13.1) LOH	60% (16/27)	[73]
RP	Microsatellite analysis: <i>RBI</i> (13q14.2) LOH	81% (22/27)	[73]
RP	Microsatellite analysis: 3pter–3p24.2, 5q21–22, 6q21–22, 7q31, 8p22, 10q23–24, 11p15.5, 16q23.1–16qter, 18q21, 18q21.33, 21q22.1–22.3 LOH	60% (12/20)	[79]
RP	Raman microspectroscopy	Accuracy, sensitivity, and specificity >85%	[80]

Abbreviations: Bx: biopsy; FISH: fluorescence in situ hybridization; IDC-P: intraductal carcinoma of the prostate; IHC: immunohistochemistry; RCP: radical cystoprostatectomy; RP: radical prostatectomy; TURP: trans-urethral resection of the prostate.

#### 4.2.1. PTEN and ERG (*TMPRSS2:ERG*)

*PTEN* is a tumour suppressor gene involved in the regulation of the cell cycle and is frequently associated with PCa aggressiveness and metastases [81–87]. Although *PTEN* loss was initially evaluated through genomic approaches, subsequent studies have shifted toward IHC as the correlation between the two is high, and some tumours presenting *PTEN* inactivation do not show genomic loss [84,88,89]. Similarly, detection of *TMPRSS2:ERG*, a fusion leading to the expression of the oncogene *ERG* in 50% of PCas [90], has moved from fluorescence in situ hybridization (FISH) to IHC [71,91,92]. Contrary to *PTEN*, *TMPRSS2:ERG* fusion or *ERG* expression has not been clearly linked to PCa outcome and is mostly used as a diagnostic marker [93–97]. Since the expression of *ERG* and *PTEN* can be evaluated by IHC, a very accessible histopathology technique, these two markers are the most studied in IDC-P [66–72,74–78,98].

In a multicentric study in 2007, Mosquera et al. [71] were the first to demonstrate that *TMPRSS2:ERG*, studied with a FISH break-apart probe, strongly correlated with IDC-P (82/87 positive cases) and CC (70/94 positive cases). Of all the morphologic features analyzed in the study, IDC-P had the strongest association with positive *TMPRSS2:ERG* fusion status (RR: 8.312, 95% CI: 2.835–24.371,  $p < 0.001$ ) [71]. Similarly, *ERG* rearrangement was identified in 75% of 48 IDC-P lesions, with 100% of concordance with adjacent carcinoma, while absent in all cases of isolated cribriform HGPIN (0/16 cases) [72]. Interestingly, most *ERG* rearrangements in IDC-P were through deletion, among which 6/36 cases showed duplication of *ERG* rearrangement in combination with deletion of 5'-*ERG*, previously associated with very poor prognosis [98]. Moreover, two cases with *ERG* rearrangement in IDC-P and lymph node metastases, showed that *ERG* status was the same in IDC-P and metastasis but discordant in another tumour foci without IDC-P [72].

It then took a few years before the first description of *PTEN* and *ERG* IHC expression in RPs by Lotan et al. in 2014 [66]. Cytoplasmic *PTEN* expression was lost in 84% (38/45) of IDC-P cases (29/38 showed uniform loss), 100% (15/15) of AIP lesions, but never in HGPIN (0/39). When *PTEN* was lost in IDC-P, at least a portion of the adjacent invasive carcinoma did not express *PTEN* in 92% of the cases. In parallel, *ERG* was expressed in 58% (26/45) of the IDC-P cases, 67% (10/15) of the AIPs and 13% (5/39) of the HGPIN lesions. The concordance levels were 100% between intraductal lesions and the adjacent invasive tumours, but not for HGPIN (of the *ERG*-positive invasive tumours, only 6% [1/11] were associated with *ERG*-positive HGPIN). Interestingly, *PTEN* was lost in 67% of *ERG*-positive tumours compared to 31% of *ERG*-negative tumours ( $p = 0.006$ ). In their subsequent biopsy study, similar proportions of expression were observed (*PTEN* loss in IDC-P: 76%, in AIP: 52%, in HGPIN: 0%; *ERG* expression in IDC-P: 58%, in AIP: 27%, in HGPIN: 0%) [67]. Lower expression of *ERG* was found in IDC-P by Schneider and Osunkoya who identified 35% (11/31) of *ERG*-positive IDC-P cases in a cohort including men who previously received androgen deprivation therapy [75], and by Nie et al. [76] who reported 10% of *ERG* positive cases in 633 consecutive cases.

In 2017, Shah et al. [68] compared the expression levels of *ERG* and *PTEN* in AIP and IDC-P in 106 prostate biopsies. They showed that *ERG* overexpression was present in 41% of AIP cases and 55% of IDC-P cases, while *PTEN* loss was observed in 71% and 72% of both lesions, respectively. In contrast, *PTEN* loss was observed in only 5% of HGPIN lesions and *ERG* was overexpressed in 16% of HGPIN foci. Concordance of *ERG* and *PTEN* expression was above 90% in IDC-P, AIP and adjacent invasive adenocarcinoma. Two years later, the same group evaluated predictors of *PTEN* loss and found that in their cohort of 260 PCas, IDC-P (HR: 4.993, 95% CI: 3.451–7.223), CC (HR: 2.459, 95% CI: 1.814–3.333) and stromagenic PCa (HR: 2.255, 95% CI: 1.634–3.112) were the best predictors of *PTEN* loss (all  $p < 0.001$ ) [78]. Furthermore, Hickman et al. obtained 100% (46/46) concordance of *ERG* status between IDC-P/AIP and nearby invasive carcinoma vs. only 7% of HGPIN cases [69]. With *PTEN* loss in two third of the cases, the concordance between IDC-P and adjacent carcinoma was 81% [69]. *PTEN* loss has also been observed in almost 90% of 40 IDC-P cases compared to 0% of 40 HGPIN cases [77].

Downes et al. [74] further verified the concordance of ERG and PTEN expression patterns in IDC-P, CC and the adjacent invasive carcinoma in a cohort of 57 PCa cases with cribriform morphology. In this cohort, ERG IHC was concordant between IDC-P, CC and adjacent invasive carcinoma in 98% of the cases (56/57). As expected, in the 44 cases with PTEN loss, 75% had heterogeneous loss. From supplemental data, IDC-P and CC staining was concordant in 86% (either retention or loss) of cases; IDC-P and adjacent acinar carcinoma staining, or CC and adjacent acinar carcinoma staining were concordant in >95% of cases, including heterogeneous loss that was concordant with either retention or loss in the other tumour compartment.

Another concordance study by Haffner et al. [70] addressed the spatial localization of ERG and PTEN status in relationship to PCa. *TMPRSS2:ERG* breakpoints analysis of seven cases showed a common phylogeny between HGPIN, PCa and IDC-P (when present), while *PTEN* loss was subclonal. Therefore, it was suggested that IDC-P represents a late event in PCa.

#### 4.2.2. Multimarker Studies

Beyond *ERG* rearrangements, Bettendorf et al. [73] showed in 2008 that IDC-P was a distinct histopathological lesion from HGPIN, as comparative genomic hybridisation (CGH) revealed chromosomal imbalances in 8/11 IDC-P cases and in 0/10 HGPIN cases, with deletions at 8p, 10q and 13q; however, invasive carcinoma was not studied.

In 2000, mutational studies were also conducted on 20 microdissected RPs to compare loss of heterozygosity (LOH) between HGPIN and IDC-P using 12 polymorphic satellite markers frequently lost in PCa, such as 8p22, 10q23–24 and 21q22.1–22.3 [79]. Briefly, LOH was more frequent in IDC-P (16%) than in Gleason pattern 4 (7%) and HGPIN (2.5%). Of note, when these results were published, CC was most likely evaluated as Gleason pattern 3 [99].

#### 4.2.3. Novel Diagnostic Biomarker: Raman Microspectroscopy

Raman spectroscopy (RS) is a nondestructive imaging technique in which the interaction between photons and tissue is measured based on different molecular bonds producing specific shifts in light wavelength [100]. Using a pen-size hand-held probe, RS can be used in real-time to detect brain tumours [101–103] or PCas on gross prostate slices [104] before integration to the da Vinci surgical robot [105]. Raman microspectroscopy ( $\mu$ RS) has also been used to differentiate prostatic cell lines and PCa from benign tissues (reviewed in [100]); however, the technique is too expensive and fastidious for clinical implementation and is meant to analyze frozen tissue, which is unavailable when clinically evaluating the histology of PCa. Accordingly, Grosset et al. [80] developed an economical  $\mu$ RS method that is performed on formalin-fixed paraffin embedded (FFPE) tissues according to standard histopathology protocols, which leads to a diagnosis within 90 min of slide preparation. Using this method, IDC-P was distinguished from invasive PCa with an accuracy, sensitivity and specificity of  $95 \pm 2\%$ ,  $96 \pm 4\%$ , and  $94 \pm 2\%$ , respectively in the training cohort. Furthermore, IDC-P could be distinguished from HGPIN with accuracies, sensitivities, and specificities of >95%. Of note, optimization of the machine-learning algorithms improved the ability to differentiate IDC-P from cancer to up to 9% [106].

#### 4.3. Cases with IDC-P Compared to Cases without IDC-P

Another important area of IDC-P research is the comparison between cases with and without IDC-P (summarized in Table 3), especially since the aforementioned studies established (mostly with ERG and PTEN expression patterns) that IDC-P was similar to its adjacent invasive carcinoma. However, most of the large-scale genomic studies of PCa were conducted before IDC-P became clinically relevant, and as such, post hoc investigations had to be performed on available frozen sections to identify IDC-P. As the distinction between IDC-P and CC is already not necessarily straightforward on FFPE slides, the low quality of the frozen sections in terms of morphology led most authors to investigate IDC-P and CC

together. Furthermore, the study context in which tissues were submitted for sequencing did not permit IHC analysis to distinguish between IDC-P and CC. Therefore, most of our genomic knowledge about the distinction between cases with and without IDC-P are based on studies comparing cases with IDC-P/CC and cases without IDC-P/CC [54,107].

**Table 3.** Overview of the studies comparing cases with IDC-P alone or in combination to cases without IDC-P. For in silico studies, selected results are presented.

N (Cohort)	Specimen	IDC-P alone or with CC	Gene or Alteration	Result	Ref.
266 (TCGA, SU2C/PCF Dream Team)	RP	IDC-P/CC vs. NC4	<i>PTEN</i> <sup>loss</sup>	39% vs. 25.5% $p = 0.024$	[54]
			<i>SPOP</i> <sup>mut</sup>	17.1% vs. 2.9% $p < 0.001$	
			<i>ATM</i> <sup>mut</sup>	7.3% vs. 0.98% $p = 0.019$	
			<i>EZH2</i> methylation	logFC= 0.48, $q < 0.001$	
			<i>TIMP2</i> methylation	logFC= −0.34, $q = 0.01$	
			<i>TIMP3</i> methylation	logFC= −0.52, $q < 0.001$	
			<i>SLIT2</i> methylation	logFC= −0.46, $q = 0.01$	
260 (TCGA)	RP	IDC-P/CC	Higher PGA: 779 gene deletions	$q$ -value $< 0.1$	[107]
			Higher PGA: 317 gene amplifications	$q$ -value $< 0.1$	
88 (TCGA)	RP	IDC-P/CC	<i>FOXA1</i> <sup>mut</sup>	15% vs. 5% $p = 0.007$	[108]
			<i>TP53</i> <sup>mut</sup>	19% vs. 10% $p = 0.035$	
			<i>SPOP</i> <sup>mut</sup>	19% vs. 10% $p = 0.035$	
277	Bx	IDC-P ( $n = 31$ )	<i>MYC</i> amplification	uOR: 2.54 95% CI: 1.10–5.88 $p = 0.02$	[108]
			<i>PTEN</i> loss	uOR: 5.01 95% CI: 2.26–11.47 $p < 0.0001$	
			<i>MYC</i> amplification and <i>PTEN</i> loss	uOR: 13.33 95% CI: 3.85–49.67 $p < 0.0001$	
91	RP	IDC-P/CC ( $n = 61$ )	<i>APC</i> methylation	Median PMR: 47.3% vs. 31.7% $p = 0.045$	[109]
			<i>RASSF15</i> methylation	Median PMR: 99.2% vs. 69.5% $p = 0.003$	
			<i>TBX15</i> methylation	Median PMR: 21.6% vs. 10.0% $p = 0.013$	
245	Liquid Bx	IDC-P	DDR pathway alterations	11.8% (19/161) vs. 2.4% (2/84) $p = 0.024$	[110]
			HR pathway alterations	11.2% (18/161) vs. 2.4% (2/84) $p = 0.032$	
			<i>NCOR2</i> alterations	21.1% (34/161) vs. 6.0% (5/84) $p = 0.004$	
7	3 RP, 3 Bx, 1 RCP	IDC-P	<i>TTF-1</i> overexpression	100% (3/3)	[110]
1	Bx	IDC-P	<i>TTF-1</i> overexpression	100% (1/1)	[110]

Abbreviations: Bx: biopsy; CC: cribriform type pattern 4; CI: confidence interval, DDR: DNA-damage repair; FC: fold change; HR: homologous repair; IDC-P: intraductal carcinoma of the prostate; NC4: non cribriform Gleason 4; PGA: percent genome altered; PMR: Percent methylation ratio; RCP: radical cystoprostatectomy; RP: radical prostatectomy; TCGA: The Cancer Genome Atlas Project; TTF-1: Thyroid transcription factor-1; uOR: univariate odds ratio.

In 277 grade group 2 biopsies, Salles et al. [108] specifically showed that PTEN loss and MYC gain were associated with the presence of IDC-P at biopsy (OR: 13.33, 95% CI: 3.85–49.67,  $p < 0.0001$ ) and that CC was larger when both alterations were present. In this study, IDC-P, large CC (>200  $\mu\text{m}$ ), as well as combined MYC gain and PTEN loss, were associated with non-organ-confined disease at RP. However, in multivariate analysis, only MYC/PTEN status remained associated with non-organ-confined disease at RP. Similarly, only MYC/PTEN status increased the area under the curve (AUC) of a model predicting non-organ-confined disease using standard prognostic factors. In this cohort, IDC-P, large CC and PTEN loss were associated with shorter time to biochemical recurrence.

In an in silico study, Böttcher et al. [107] showed that the percentage of genome alterations in PCas from men included in The Cancer Genome Atlas Project (TCGA) and in the Canadian Prostate Cancer Genome Network (CPC-GENE) was three-fold higher in men with IDC-P/CC, and included deletions and amplifications in regions previously associated with aggressive PCa, such as 8p deletions (*NKX3.1*), 10q23 deletions (*PTEN*) and 8q amplifications (*MYC*).

In a similar in silico study, Elfandy et al. [54] assessed the alterations associated with IDC-P/CC compared to non-CC Gleason pattern 4 in the TCGA and SU2C/PCF Dream Team cohorts. IDC-P/CC remained significantly associated with deletions at 8p21–22, 6q21, 11q22–23 and 10q23 and gains at 3q11–29 while controlling for percentage of genome alterations and Gleason score. *PTEN* loss was significantly enriched in IDC-P/CC (OR: 1.87, 95% CI: 1.09–3.26,  $p = 0.024$ ). *SPOP* and *ATM* mutations were significantly more frequent in IDC-P/CC than in non-CC Gleason pattern 4, but the frequency of *ERG* fusions was not different between the two groups. Moreover, gene expression profiles of IDC-P/CC showed upregulation of the *mTORC1* and *MYC* pathways and hypermethylation in *CYP26A1*.

Additionally, Olkhov-Mitsel et al. [109] investigated the methylation profile of *ALU*, *APC*, *CYP26A1*, *HOXD3*, *HOXD8*, *RASSF1*, *TBX15*, *TGF- $\beta$*  in IDC-P/CC lesions from 91 Gleason score 7 PCas and found an increase in the methylation levels of *APC*, *RASSF15* and *TBX15* in IDC-P/CC.

Lastly, patients with IDC-P have also been characterized for genomic alterations in a study using liquid biopsies targeting PCa-related genes in a cohort of 245 men with M0 disease, metastatic hormone-sensitive PCas and CRPC [110]. Zhao et al. showed that despite similar mutational rates in the *AR* pathway between men with and without IDC-P, the IDC-P group showed enrichment of alterations of the *AR* negative regulator *NCOR2*. Furthermore, cases with a higher amount of IDC-P harboured more *AR* mutations.

Anecdotally, IDC-P has been shown to sometimes harbour small cell-like changes, which can be shown by expression of thyroid transcription factor (TTF-1) in IDC-P [111,112].

#### 4.4. IDC-P and Deleterious Germline and Somatic Alterations of DNA-Damage Repair Genes

Since germline mutations of the *BRCA2* tumour suppressor gene significantly increase the likelihood of developing aggressive PCas [113–116], many researchers have investigated the link between IDC-P and deleterious germline mutations (Table 4). With the emergence of targeted therapies for men with alterations in DDR genes, histology can help preselect patients who are more likely to benefit from these treatments [117–119]. According to the following studies, the National Comprehensive Cancer Network (NCCN) PCa guidelines include IDC-P as an indication to search for mutations in DDR genes [120].

**Table 4.** Overview of the studies associating IDC-P to deleterious germline and somatic alterations of DNA-damage repair genes.

Specimen	Method	Alteration	Result	Ref.
PDX	Histology review	IDC-P in <i>BRCA2</i> <sup>mut</sup> and BRCAX grafts vs. sporadic PCas	61% (27/44) vs. 8% (5/62) $p = 0.04$	[121]
RP	Microdissection and WGS	In <i>BRCA2</i> <sup>mut</sup> cases <i>MED12L/MED12</i> amplification in IDC-P+ vs. –	75% (6/8) vs. 17% (1/6)	[122]
Saliva	NGS	% IDC-P in cases with and without germline mutations of DDR genes	24% (5/21) vs. 9% (12/129) $p = 0.06$	[123]
Saliva	NGS	% IDC-P in cases with germline mutations of MMR genes	23% (3/13 IDC-P+)	[124]
6 Bx, 6 RP, 1 LN (IDC-P = 3)	NGS	<i>MSH6</i> germline mutation in IDC-P cases	1/3	[124]
		<i>MSH6</i> somatic mutations in IDC-P cases	1/3	
		<i>TP53</i> somatic mutations in IDC-P cases	1/3	
		<i>MSH2</i> somatic mutation + LOH in IDC-P cases	1/3	
		<i>MSH6</i> somatic mutation + LOH in IDC-P cases	1/3	
135 RP, 39 Bx (IDC-P = 79)	FISH	Bi-allelic <i>BRCA2</i> loss ( <i>LOH + gBRCA2</i> or <i>bi-allelicDel</i> )	mOR: 4.3 95% CI: 1.1–16.2 $p = 0.031$	[125]
		<i>PTEN</i> homozygous loss	mOR: 5.2 95% CI: 2.1–13.1 $p < 0.001$	

Abbreviations: BRCAX: familial history of prostate cancer without identified *BRCA2* mutations; Bx: biopsy; CI: confidence interval; DDR: DNA-damage repair; Del: deletion; FISH: fluorescence in situ hybridization; IDC-P: intraductal carcinoma of the prostate; LN: lymph node; LOH: loss of heterozygosity; MMR: mismatch repair; mOR: multivariate odds ratio; NGS: next-generation sequencing; PCa: prostate cancer; PDX: patient-derived xenograft; RP: radical prostatectomy; WGS: whole-genome sequencing.

The link between IDC-P and *BRCA2* mutations was first established in 2014 by Risbridger et al. [121]. In their study, they observed high incidence of IDC-P (61%) in 44 patient-derived xenografts (PDXs) from three *BRCA2* carriers, and from one man with a familial history of cancer but without identified *BRCA* mutation (BRCAX), compared to the incidence of IDC-P (8%) in 62 PDXs derived from 12 men with sporadic PCas. Following this observation, they evaluated PCa specimens from 33 *BRCA2* carriers, 62 BRCAX cases and 32 sporadic PCa cases. In this cohort, the incidence of IDC-P was significantly higher in *BRCA2* carriers (42%) compared with sporadic PCa cases (3/32, 9%) ( $p = 0.004$ ). While 26% of BRCAX patients exhibited IDC-P, the incidence was not statistically significant compared with sporadic PCa cases. In men of the *BRCA* and BRCAX groups, the presence of IDC-P was associated with shorter overall survival (HR: 16.9,  $p = 0.0064$  and HR: 3.57,  $p = 0.0086$ , respectively), without any difference between men with IDC-P from the two groups ( $p = 0.35$ ). Of note, because of the low numbers, the effect of IDC-P in men with sporadic PCas could not be compared to the effect of IDC-P in men with *BRCA2*/*BRCAX* profiles.

In 2017, Taylor et al. [122] associated IDC-P with CNAs portending poor prognosis, such as *BCL6* gain or *MTOR* loss in men with PCas associated with a germline *BRCA2* mutation. In this study, IDC-P and adjacent invasive carcinoma phylogenies were also evaluated in four carriers of germline *BRCA2* mutations and six sporadic PCas. In both groups, IDC-P and the adjacent invasive carcinoma arose from the same clone, leaving no information about the original tumour focus, and *MYC* amplifications were found with high frequencies. However, in the sporadic group, these *MYC* amplifications were

present in both tumour compartments in only one case. Furthermore, in the same study, 14 men carrying a deleterious germline mutant *BRCA2* allele were compared to 200 age-matched men with localized PCas to investigate the genomic alterations underlying the aggressiveness of *BRCA2*-mutated PCa. Potential identified drivers of aggressiveness included an amplification of a region of chromosome 3q containing the WNT/ $\beta$ -catenin pathway modulator *MED12L* and an amplification of *MED*, the *MED12L* homolog. These were found in 66% and 44% of the *BRCA2*-mutated cases, respectively. Interestingly, *MED12L/MED12* amplification in PCa, already associated with poor outcomes [126,127], was observed more frequently in IDC-P (75% vs. 17%), and these mutations were not enriched in sporadic tumours with IDC-P [122].

The association between IDC-P and DDR genes has been further investigated in a series of 150 consecutive patients with metastatic or recurrent PCas [123]. IDC-P tended to be more prevalent in men with germline DDR gene alterations compared to men without alterations (24% (5/21) vs. 9% (12/129),  $p = 0.06$ ). The same group then performed an exploratory study and found that from 13 men with pathogenic mismatch-repair (MMR) gene mutations (10 from somatic screening, three from germline screening), three had ductal or IDC-P histologies (23%) compared to 14 out of 114 MMR-proficient men (12%) ( $p = 0.38$ , Fisher's exact test) [124].

In a further study of 58 men who were carriers of a germline *BRCA2* mutation matched with 116 non-carriers [125], Lozano et al. observed that the presence of IDC-P features was similar between carriers and non-carriers (36% vs. 50%,  $p = 0.085$ ). However, bi-allelic mutations, or somatic plus germline mutations were found at higher frequencies in men with IDC-P (43% vs. 12%,  $p < 0.001$ ), with similar proportions for men with CC. Of note, in this study, *PTEN* homozygous loss was more prevalent in IDC-P than in CC [125].

Lastly, in the previously mentioned cohort from Zhao et al. that included men with M0 disease, metastatic hormone-sensitive PCas and CRPC [110], patients with and without IDC-P shared a similar germline mutation rate as evaluated by liquid biopsy. However, patients with IDC-P had more frequent germline pathogenic alterations in DDR genes (12% vs. 2%,  $p = 0.024$ ) and homologous recombination genes (11% vs. 2%,  $p = 0.032$ ). Interestingly, the frequencies of DDR mutations increased as PCa without IDC-P progressed from M0 disease to CRPC, but was consistently high in men with IDC-P. All *BRCA2* mutations were identified in men with IDC-P.

#### 4.5. IDC-P and Its Impact on PCa Outcome

Besides the above-mentioned study by Risbringer et al. [121], few groups have addressed the molecular features underlying the aggressivity of IDC-P [30,128–130] (Table 5). Increasing our knowledge in this field will be central to the development of new therapies for men with IDC-P.

**Table 5.** Overview of the studies evaluating the impact of the molecular characteristics of IDC-P alone or in combination on prostate cancer outcome in radical prostatectomies.

N	IDC-P alone or with CC	Method	Measure	Result	Ref.
476	IDC-P/CC	CNA analysis	PGA	34% vs. 16% $p = 0.033$	[30]
156	IDC-P/CC	Microarray analysis	<i>SCHLAP1</i> expression	FC 3.23 $p < 0.001$	
393	IDC-P/CC	RNA-ISH	Detection of IDC-P/CC using <i>SCHLAP1</i> expression	Accuracy: 82.4% $p < 0.001$	[128]
318	IDC-P/CC	SNP microarray	PGA	$p < 0.0001$	
333 (TCGA) and 215 (CPC-GENE)	IDC-P/CC	Ragnum signature	Hypoxia	$p < 0.0001$	

Table 5. Cont.

N	IDC-P alone or with CC	Method	Measure	Result	Ref.
144	IDC-P/CC	Total RNA-seq	<i>SCHLAP1:UBE2E3</i> fusion	FDR:0.0015	[129]
163	IDC-P	IHC	PTEN protein loss	86% (30/35)	[130]
	IDC-P/CC	IHC	BCR cumulative incidence	mHR: 5.06, 95%CI: 2.21–11.6 $p < 0.001$	

Abbreviations: CC: cribriform type pattern 4; CI: confidence interval; CNA: copy number alteration; CPC-GENE: Canadian Prostate Cancer Genome-Network; FC: fold change; IDC-P: intraductal carcinoma of the prostate; IHC: immunohistochemistry; mHR: multivariate hazard ratio; PGA: percent genome altered; RNA-ISH: RNA in situ hybridization; RP: radical prostatectomy; TCGA: The Cancer Genome Atlas Project.

In 2017, Chua et al. [30] evaluated whether IDC-P/CC was associated with hypoxia and genomic instability. In addition to demonstrating an increased risk of metastasis in men with IDC-P/CC (see above), Chua et al. showed that IDC-P/CC tumours harboured a higher percentage of genome alterations (34% vs. 16%,  $p = 0.033$ ), with a nonsignificant increase in the hypoxic tumour subpopulation (64% vs. 45%,  $p = 0.17$ ). In a subsequent study by the same group, a hypoxia signature was significantly associated with IDC-P/CC [128]. Furthermore, Chua et al. [30] showed that men with IDC-P/CC and a high percentage of genome alteration were more likely to develop distant metastasis (HR: 5.5, 95% CI: 2.5–12.2,  $p < 0.0001$ ). Importantly, only one gene was found to be overexpressed in IDC-P/CC-positive tumours: *SChLAP1*, a long non-coding RNA associated with poor outcome in PCa [131,132]. In this cohort [30], men with *SChLAP1* overexpression and IDC-P/CC experienced earlier biochemical recurrence compared to men without IDC-P/CC and without *SChLAP1* overexpression (HR: 2.6, 95% CI: 1.4–4.7,  $p = 0.0027$ ). In a subsequent study, *SCHLAP1:UBE2E3* fusion was highly associated with IDC-P/CC and was found to be enriched in metastases [129].

Very recently, Spieker et al. [130] identified PTEN loss in 86% of IDC-P cases (30/35 RPs) and in 64% of CC lesions (72/112 RPs). In this study, CC was associated with shorter time to biochemical recurrence (multivariate HR: 3.50, 95% CI: 1.89–6.49,  $p < 0.001$ ) but not IDC-P alone. However, combining both was associated with a higher cumulative incidence of biochemical recurrence (multivariate HR: 5.06, 95% CI: 2.21–11.6,  $p < 0.001$ ).

#### 4.6. Commercial Classification Assays

An important last question that has been only recently addressed is the association between IDC-P and commercial risk-classification assays (Table 6). We believe this question will become increasingly relevant to the care of men with PCa.

Table 6. Overview of the studies evaluating the association between IDC-P and commercial risk-stratification assays.

N	Specimen	IDC-P alone or with CC	Measure	Result	Ref.
319	Bx	IDC-P/CC	Increase in GPS	No Gleason pattern 4: mean GPS = 22.3; IDC-P/CC: mean GPS = 41.8 $p < 0.001$	[133]
48	RP	IDC-P/CC	% cases with high-risk Decipher score	56% vs. 22% $p = 0.007$	[134]
		IDC-P	Increase in Decipher score	OR: 1.92, 95% CI: 0.65–5.67, $p = 0.24$	

Abbreviations: CC: cribriform carcinoma; CI: confidence interval; GPS: Oncotype Dx Genomic Prostate Score®; IDC-P: intraductal carcinoma of the prostate; OR: Odds ratio.

The Oncotype DX Genomic Prostate Score (GPS) assay uses biopsy samples to provide a score ranging from 0 to 100 for men with PCa, to predict the probability of adverse pathology at RP, biochemical recurrence at 3 years and metastasis and PCa-related death at 10 years [135–138]. In their study including 296 men with a total of 319 prostate biopsies,

Greenland et al. [133] showed that among different Gleason pattern 4 tumours, the IDC-P/CC pattern was associated with the highest increase in the GPS, with a mean GPS of 42. Of note, three authors of this study, including the senior author, reported financial interest and/or a relationship with Genomic Health (provider of the Oncotype DX platform).

The Decipher Prostate Cancer Test (GenomeDX Biosciences) is a 22 gene-expression assay that produces a continuous score between 0 and 1 to predict the outcomes of PCa patients at initial prostate biopsy [139,140] and for those who undergo RP [141,142]. This risk stratification method predicts the likelihood of developing metastasis within 5 or 10 years [142–152] and cancer-specific mortality [146,153], thus impacting physician-patient decision making and subsequent patient management [154–159]. In a study of 48 men who underwent RP and lymph node dissection for PCa, the Decipher test was used in cases with pT3 disease and/or positive surgical margins and showed that both the presence of IDC-P and CC (OR: 1.92, 95% CI: 0.65–5.67,  $p = 0.24$  and OR: 9.60, 95% CI: 1.48–62.16,  $p = 0.02$ , respectively) increased the Decipher risk classification, although the increase associated with IDC-P was not statistically significant ( $n = 15$ ) [134].

## 5. Conclusions

From the reviewed data, IDC-P is clearly an important factor in the survival of men with PCa and seems to have important effects on response to standard treatments. However, as data about IDC-P are still emerging, organizations have proposed different criteria to diagnose IDC-P in histopathological specimens [160]. The ISUP suggests including IDC-P in the tumour grade with CC [161], whereas the Genitourinary Pathology Society (GUPS) recommends including IDC-P in the tumour volume estimation but excluding it from the tumour grade [10]. While this review was not meant to evaluate grading issues associated with IDC-P, the controversy surrounding the diagnosis of IDC-P highlights the need for more research to characterize the prognostic effect of IDC-P.

Although our molecular knowledge about IDC-P has advanced in recent years, most of it has come from studies that evaluated ERG and PTEN status of IDC-P or from post hoc histological reviews of PCas in large sequencing studies that evaluated the characteristics of IDC-P/CC together. Since its initial description in 1985 by Kovi et al. [7], the research questions that need to be addressed about IDC-P are still numerous and of high clinical relevance.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/article/10.3390/cancers14030820/s1>, Table S1: (A) IDC-P predicts the presence of lymph node metastasis at diagnosis; (B) IDC-P predicts the occurrence of distant metastasis. (C) IDC-P predicts poor prognosis in men with metastatic PCa; (D) IDC-P predicts death from prostate cancer; Table S2: Treatment response in men with IDC-P alone or in combination with CC.

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## References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. *CA Cancer J. Clin.* **2021**, *71*, 7–33. [[CrossRef](#)] [[PubMed](#)]
2. Tsuzuki, S.; Park, S.H.; Eber, M.R.; Peters, C.M.; Shiozawa, Y. Skeletal complications in cancer patients with bone metastases. *Int. J. Urol.* **2016**, *23*, 825–832. [[CrossRef](#)] [[PubMed](#)]
3. Jin, J.K.; Dayyani, F.; Gallick, G.E. Steps in prostate cancer progression that lead to bone metastasis. *Int. J. Cancer* **2011**, *128*, 2545–2561. [[CrossRef](#)] [[PubMed](#)]
4. Epstein, J.I.; Egevad, L.; Amin, M.B.; Delahunt, B.; Srigley, J.R.; Humphrey, P.A. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am. J. Surg. Pathol.* **2015**, *40*, 244–252. [[CrossRef](#)] [[PubMed](#)]
5. McNeal, J.E.; Yemoto, C.E. Spread of adenocarcinoma within prostatic ducts and acini. Morphologic and clinical correlations. *Am. J. Surg. Pathol.* **1996**, *20*, 802–814. [[CrossRef](#)]
6. Rhamy, R.K.; Buchanan, R.D.; Spalding, M.J. Intraductal carcinoma of the prostate gland. *J. Urol.* **1973**, *109*, 457–460. [[CrossRef](#)]
7. Kovi, J.; Jackson, M.A.; Heshmat, M.Y. Ductal spread in prostatic carcinoma. *Cancer* **1985**, *56*, 1566–1573. [[CrossRef](#)]
8. Porter, L.H.; Lawrence, M.G.; Ilic, D.; Clouston, D.; Bolton, D.M.; Frydenberg, M.; Murphy, D.G.; Pezaro, C.; Risbridger, G.P.; Taylor, R.A. Systematic Review Links the Prevalence of Intraductal Carcinoma of the Prostate to Prostate Cancer Risk Categories. *Eur. Urol.* **2017**, *72*, 492–495. [[CrossRef](#)]
9. Seipel, A.H.; Wiklund, F.; Wiklund, N.P.; Egevad, L. Histopathological features of ductal adenocarcinoma of the prostate in 1,051 radical prostatectomy specimens. *Virchows Arch.* **2013**, *462*, 429–436. [[CrossRef](#)]
10. Epstein, J.I.; Amin, M.B.; Fine, S.W.; Algaba, F.; Aron, M.; Baydar, D.E.; Beltran, A.L.; Brimo, F.; Cheville, J.C.; Coicchia, M.; et al. The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer. *Arch. Pathol. Lab. Med.* **2021**, *145*, 461–493. [[CrossRef](#)]
11. van Leenders, G.; van der Kwast, T.H.; Iczkowski, K.A. The 2019 International Society of Urological Pathology Consensus Conference on Prostate Cancer Grading. *Eur. Urol.* **2021**, *79*, 707–709. [[CrossRef](#)]
12. Varma, M. Intraductal Carcinoma of the Prostate: A Guide for the Practicing Pathologist. *Adv. Anat. Pathol.* **2021**, *28*, 276–287. [[CrossRef](#)]
13. Zhang, Y.C.; Sun, G.L.; Ma, D.L.; Wei, C.; Shang, H.J.; Liu, Z.; Li, R.; Wang, T.; Wang, S.G.; Liu, J.H.; et al. The presence of intraductal carcinoma of the prostate is closely associated with poor prognosis: A systematic review and meta-analysis. *Asian J. Androl.* **2021**, *23*, 103–108. [[CrossRef](#)]
14. Karakoc, S.; Celik, S.; Kaya, N.; Bozkurt, O.; Ellidokuz, H.; Tuna, B.; Yorukoglu, K.; Mungan, M.U. Prognostic value of intraductal carcinoma for adjuvant radiotherapy candidates after radical prostatectomy. *Int. J. Clin. Pract.* **2021**, *75*, e14099. [[CrossRef](#)]
15. Trinh, V.Q.; Benzerdjeb, N.; Chagnon-Monarque, S.; Dionne, N.; Delouya, G.; Kougioumoutzakakis, A.; Sirois, J.; Albadine, R.; Latour, M.; Mes-Masson, A.-M.; et al. Retrospective study on the benefit of adjuvant radiotherapy in men with intraductal carcinoma of prostate. *Radiat. Oncol.* **2019**, *14*, 60. [[CrossRef](#)] [[PubMed](#)]
16. Porter, L.H.; Hashimoto, K.; Lawrence, M.G.; Pezaro, C.; Clouston, D.; Wang, H.; Papargiris, M.; Thorne, H.; Li, J.; kConFab; et al. Intraductal carcinoma of the prostate can evade androgen deprivation, with emergence of castrate-tolerant cells. *BJU Int.* **2018**, *121*, 971–978. [[CrossRef](#)]
17. Chen, Z.; Chen, N.; Shen, P.; Gong, J.; Li, X.; Zhao, T.; Liao, B.; Liu, L.; Liu, Z.; Zhang, X.; et al. The presence and clinical implication of intraductal carcinoma of prostate in metastatic castration resistant prostate cancer. *Prostate* **2015**, *75*, 1247–1254. [[CrossRef](#)] [[PubMed](#)]
18. Abascal-Junquera, J.M.; Fumado-Ciutat, L.; Gasa-Galmes, B.; Costa-Planells, M.; Munarriz-Polo, M.; Sanroma-Salva, A.; Polaina-Barroso, L.; Sola-Marques, C.; Juanpere-Rodero, N.; Lloreta-Trull, J.; et al. Concomitant intraductal carcinoma of the prostate and response to hormonal therapy in metastatic prostate carcinoma. *Actas. Urol. Esp.* **2021**, *45*, 455–460. [[CrossRef](#)] [[PubMed](#)]
19. O'Brien, C.; True, L.D.; Higan, C.S.; Rademacher, B.L.; Garzotto, M.; Beer, T.M. Histologic changes associated with neoadjuvant chemotherapy are predictive of nodal metastases in patients with high-risk prostate cancer. *Am. J. Clin. Pathol.* **2010**, *133*, 654–661. [[CrossRef](#)]
20. Xu, N.; Ke, Z.B.; Chen, Y.H.; Wu, Y.P.; Chen, S.H.; Wei, Y.; Zheng, Q.S.; Huang, J.B.; Li, X.D.; Xue, X.Y. Risk Factors for Pathologically Confirmed Lymph Nodes Metastasis in Patients With Clinical T2N0M0 Stage Prostate Cancer. *Front. Oncol.* **2020**, *10*, 1547. [[CrossRef](#)] [[PubMed](#)]
21. Kryvenko, O.N.; Gupta, N.S.; Virani, N.; Schultz, D.; Gomez, J.; Amin, A.; Lane, Z.; Epstein, J.I. Gleason score 7 adenocarcinoma of the prostate with lymph node metastases: Analysis of 184 radical prostatectomy specimens. *Arch. Pathol. Lab. Med.* **2013**, *137*, 610–617. [[CrossRef](#)] [[PubMed](#)]
22. Downes, M.R.; Xu, B.; van der Kwast, T.H. Gleason grade patterns in nodal metastasis and corresponding prostatectomy specimens: Impact on patient outcome. *Histopathology* **2019**, *75*, 715–722. [[CrossRef](#)] [[PubMed](#)]
23. Downes, M.R.; Xu, B.; van der Kwast, T.H. Cribriform architecture prostatic adenocarcinoma in needle biopsies is a strong independent predictor for lymph node metastases in radical prostatectomy. *Eur. J. Cancer* **2021**, *148*, 432–439. [[CrossRef](#)] [[PubMed](#)]
24. Lindberg, J.; Kristiansen, A.; Wiklund, P.; Gronberg, H.; Egevad, L. Tracking the origin of metastatic prostate cancer. *Eur. Urol.* **2015**, *67*, 819–822. [[CrossRef](#)] [[PubMed](#)]
25. Dinerman, B.F.; Khani, F.; Golan, R.; Bernstein, A.N.; Cosiano, M.F.; Margolis, D.J.; Hu, J.C. Population-based study of the incidence and survival for intraductal carcinoma of the prostate. *Urol. Oncol.* **2017**, *35*, 673.e9–673.e14. [[CrossRef](#)] [[PubMed](#)]

26. Trinh, V.Q.; Sirois, J.; Benzerdjeb, N.; Mansoori, B.K.; Grosset, A.A.; Albadine, R.; Latour, M.; Mes-Masson, A.M.; Hovington, H.; Bergeron, A.; 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. [[CrossRef](#)]
27. Tom, M.C.; Nguyen, J.K.; Luciano, R.; Mian, O.Y.; Stephans, K.L.; Ciezki, J.P.; Smile, T.D.; Wei, W.; McKenney, J.K.; Magi-Galluzzi, C.; et al. Impact of Cribriform Pattern and Intraductal Carcinoma on Gleason 7 Prostate Cancer Treated with External Beam Radiotherapy. *J. Urol.* **2019**, *202*, 710–716. [[CrossRef](#)]
28. Van der Kwast, T.; Al Daoud, N.; Collette, L.; Sykes, J.; Thoms, J.; Milosevic, M.; Bristow, R.G.; Van Tienhoven, G.; Warde, P.; Mirimanoff, R.O.; 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*, 1318–1325. [[CrossRef](#)]
29. Kweldam, C.F.; Wildhagen, M.F.; Steyerberg, E.W.; Bangma, C.H.; van der Kwast, T.H.; van Leenders, G.J. Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. *Mod. Pathol.* **2015**, *28*, 457–464. [[CrossRef](#)]
30. Chua, M.L.K.; Lo, W.; Pintilie, M.; Murgic, J.; Lalonde, E.; Bhandari, V.; Mahamud, O.; Gopalan, A.; Kweldam, C.F.; van Leenders, G.; et al. A Prostate Cancer "Nimbus": Genomic Instability and SchLAP1 Dysregulation Underpin Aggression of Intraductal and Cribriform Subpathologies. *Eur. Urol.* **2017**, *72*, 665–674. [[CrossRef](#)]
31. Kimura, K.; Tsuzuki, T.; Kato, M.; Saito, A.M.; Sassa, N.; Ishida, R.; Hirabayashi, H.; Yoshino, Y.; Hattori, R.; Gotoh, M. Prognostic value of intraductal carcinoma of the prostate in radical prostatectomy specimens. *Prostate* **2014**, *74*, 680–687. [[CrossRef](#)] [[PubMed](#)]
32. Hansum, T.; Hollemans, E.; Verhoef, E.I.; Bangma, C.H.; Rietbergen, J.; Osanto, S.; Pelger, R.C.M.; van Wezel, T.; van der Poel, H.; Bekers, E.; et al. Comedonecrosis Gleason pattern 5 is associated with worse clinical outcome in operated prostate cancer patients. *Mod. Pathol.* **2021**, *34*, 2064–2070. [[CrossRef](#)] [[PubMed](#)]
33. Hollemans, E.; Verhoef, E.I.; Bangma, C.H.; Rietbergen, J.; Osanto, S.; Pelger, R.C.M.; van Wezel, T.; van der Poel, H.; Bekers, E.; Helleman, J.; et al. Cribriform architecture in radical prostatectomies predicts oncological outcome in Gleason score 8 prostate cancer patients. *Mod. Pathol.* **2021**, *34*, 184–193. [[CrossRef](#)] [[PubMed](#)]
34. Hollemans, E.; Verhoef, E.I.; Bangma, C.H.; Rietbergen, J.; Roobol, M.J.; Helleman, J.; van Leenders, G. 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*, 755–762. [[CrossRef](#)]
35. Velho, P.I.; Lim, D.; Wang, H.; Park, J.C.; Kaur, H.B.; Almutairi, F.; Carducci, M.A.; Denmeade, S.R.; Markowski, M.C.; Isaacs, W.B.; et al. Molecular Characterization and Clinical Outcomes of Primary Gleason Pattern 5 Prostate Cancer After Radical Prostatectomy. *JCO Precis. Oncol.* **2019**, *3*, PO.19.00081. [[CrossRef](#)]
36. Zhao, T.; Liao, B.; Yao, J.; Liu, J.; Huang, R.; Shen, P.; Peng, Z.; Gui, H.; Chen, X.; Zhang, P.; et al. Is there any prognostic impact of intraductal carcinoma of prostate in initial diagnosed aggressively metastatic prostate cancer? *Prostate* **2015**, *75*, 225–232. [[CrossRef](#)]
37. Zhao, J.; Shen, P.; Sun, G.; Chen, N.; Liu, J.; Tang, X.; Huang, R.; Cai, D.; Gong, J.; Zhang, X.; 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*, 55374–55383. [[CrossRef](#)] [[PubMed](#)]
38. Zhao, J.; Liu, J.; Sun, G.; Zhang, M.; Chen, J.; Shen, P.; Liu, Z.; Liao, B.; Zhang, X.; Gong, J.; 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*, 759–768. [[CrossRef](#)] [[PubMed](#)]
39. Zhao, J.; Sun, G.; Liao, B.; Zhang, X.; Armstrong, C.M.; Yin, X.; Liu, J.; Chen, J.; Yang, Y.; Zhao, P.; et al. Novel nomograms for castration-resistant prostate cancer and survival outcome in patients with de novo bone metastatic prostate cancer. *BJU Int.* **2018**, *122*, 994–1002. [[CrossRef](#)] [[PubMed](#)]
40. Kato, M.; Tsuzuki, T.; Kimura, K.; Hirakawa, A.; Kinoshita, F.; Sassa, N.; Ishida, R.; Fukatsu, A.; Kimura, T.; Funahashi, Y.; et al. The presence of intraductal carcinoma of the prostate in needle biopsy is a significant prognostic factor for prostate cancer patients with distant metastasis at initial presentation. *Mod. Pathol.* **2016**, *29*, 166–173. [[CrossRef](#)]
41. Kato, M.; Hirakawa, A.; Sato, H.; Hanazawa, R.; Naito, Y.; Tochigi, K.; Sano, T.; Ishida, S.; Funahashi, Y.; Fujita, T.; et al. Grade group 2 (10%  $\geq$  GP4) patients have very similar malignant potential with grade group 1 patients, given the risk of intraductal carcinoma of the prostate. *Int. J. Clin. Oncol.* **2021**, *26*, 764–769. [[CrossRef](#)]
42. Kato, M.; Kimura, K.; Hirakawa, A.; Kobayashi, Y.; Ishida, R.; Kamihira, O.; Majima, T.; Funahashi, Y.; Sassa, N.; Matsukawa, Y.; et al. Prognostic parameter for high risk prostate cancer patients at initial presentation. *Prostate* **2018**, *78*, 11–16. [[CrossRef](#)] [[PubMed](#)]
43. Saeter, T.; Vlatkovic, L.; Waaler, G.; Servoll, E.; Nesland, J.M.; Axcrone, K.; Axcrone, U. Intraductal Carcinoma of the Prostate on Diagnostic Needle Biopsy Predicts Prostate Cancer Mortality: A Population-Based Study. *Prostate* **2017**, *77*, 859–865. [[CrossRef](#)] [[PubMed](#)]
44. Arai, Y.; Kanamaru, H.; Yoshimura, K.; Okubo, K.; Kamoto, T.; Yoshida, O. Incidence of lymph node metastasis and its impact on long-term prognosis in clinically localized prostate cancer. *Int. J. Urol.* **1998**, *5*, 459–465. [[CrossRef](#)] [[PubMed](#)]
45. Tsuzuki, T. Intraductal carcinoma of the prostate: A comprehensive and updated review. *Int. J. Urol.* **2015**, *22*, 140–145. [[CrossRef](#)] [[PubMed](#)]

46. Miura, N.; Mori, K.; Mostafaei, H.; Quhal, F.; Motlagh, R.S.; Pradere, B.; Laukhtina, E.; D'Andrea, D.; Saika, T.; Shariat, S.F. The Prognostic Impact of Intraductal Carcinoma of the Prostate: A Systematic Review and Meta-Analysis. *J. Urol.* **2020**, *204*, 909–917. [[CrossRef](#)]
47. Iczkowski, K.A.; van Leenders, G.; Tarima, S.; Wu, R.; Van der Kwast, T.; Berney, D.M.; Evans, A.J.; Wheeler, T.M.; Ro, J.Y.; Samaratunga, H.; et al. Cribriform prostate cancer: Morphologic criteria enabling a diagnosis, based on survey of experts. *Ann. Diagn. Pathol.* **2021**, *52*, 151733. [[CrossRef](#)] [[PubMed](#)]
48. Iczkowski, K.A.; Paner, G.P.; Van der Kwast, T. The New Realization About Cribriform Prostate Cancer. *Adv. Anat. Pathol.* **2018**, *25*, 31–37. [[CrossRef](#)] [[PubMed](#)]
49. Rubin, M.A.; de La Taille, A.; Bagiella, E.; Olsson, C.A.; O'Toole, K.M. Cribriform carcinoma of the prostate and cribriform prostatic intraepithelial neoplasia: Incidence and clinical implications. *Am. J. Surg. Pathol.* **1998**, *22*, 840–848. [[CrossRef](#)]
50. Efstathiou, E.; Abrahams, N.A.; Tibbs, R.F.; Wang, X.; Pettaway, C.A.; Pisters, L.L.; Mathew, P.F.; Do, K.A.; Logothetis, C.J.; Troncoso, P. Morphologic characterization of preoperatively treated prostate cancer: Toward a post-therapy histologic classification. *Eur. Urol.* **2010**, *57*, 1030–1038. [[CrossRef](#)]
51. Kato, M.; Hirakawa, A.; Kobayashi, Y.; Yamamoto, A.; Ishida, R.; Kamihira, O.; Sano, T.; Majima, T.; Ishida, S.; Funahashi, Y.; et al. Response of intraductal carcinoma of the prostate to androgen deprivation therapy predicts prostate cancer prognosis in radical prostatectomy patients. *Prostate* **2020**, *80*, 284–290. [[CrossRef](#)]
52. McKay, R.R.; Xie, W.; Ye, H.; Fennessy, F.M.; Zhang, Z.; Lis, R.; Calagua, C.; Rathkopf, D.; Laudone, V.P.; Bublely, G.J.; et al. Results of a Randomized Phase II Trial of Intense Androgen Deprivation Therapy prior to Radical Prostatectomy in Men with High-Risk Localized Prostate Cancer. *J. Urol.* **2021**, *206*, 80–87. [[CrossRef](#)] [[PubMed](#)]
53. Hollemans, E.; Verhoef, E.I.; Bangma, C.H.; Rietbergen, J.; Helleman, J.; Roobol, M.J.; van Leenders, G. Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis. *Mod. Pathol.* **2019**, *32*, 139–146. [[CrossRef](#)] [[PubMed](#)]
54. Elfandy, H.; Armenia, J.; Pederzoli, F.; Pullman, E.; Pertega-Gomes, N.; Schultz, N.; Viswanathan, K.; Vosoughi, A.; Blattner, M.; Stopsack, K.H.; et al. Genetic and Epigenetic Determinants of Aggressiveness in Cribriform Carcinoma of the Prostate. *Mol. Cancer Res.* **2019**, *17*, 446–456. [[CrossRef](#)] [[PubMed](#)]
55. Alberts, A.R.; Bokhorst, L.P.; Kweldam, C.F.; Schoots, I.G.; van der Kwast, T.H.; van Leenders, G.J.; Roobol, M.J. Biopsy undergrading in men with Gleason score 6 and fatal prostate cancer in the European Randomized study of Screening for Prostate Cancer Rotterdam. *Int. J. Urol.* **2017**, *24*, 281–286. [[CrossRef](#)] [[PubMed](#)]
56. McKay, R.R.; Berchuck, J.; Kwak, L.; Xie, W.; Silver, R.; Bublely, G.J.; Chang, P.K.; Wagner, A.; Zhang, Z.; Kibel, A.S.; et al. Outcomes of Post-Neoadjuvant Intense Hormone Therapy and Surgery for High Risk Localized Prostate Cancer: Results of a Pooled Analysis of Contemporary Clinical Trials. *J. Urol.* **2021**, *205*, 1689–1697. [[CrossRef](#)]
57. Wilkinson, S.; Ye, H.; Karzai, F.; Harmon, S.A.; Terrigino, N.T.; VanderWeele, D.J.; Bright, J.R.; Atway, R.; Trostel, S.Y.; Carrabba, N.V.; et al. Nascent Prostate Cancer Heterogeneity Drives Evolution and Resistance to Intense Hormonal Therapy. *Eur. Urol.* **2021**, *80*, 746–757. [[CrossRef](#)] [[PubMed](#)]
58. Yamamoto, A.; Kato, M.; Matsui, H.; Ishida, R.; Kimura, T.; Funahashi, Y.; Sassa, N.; Matsukawa, Y.; Kamihira, O.; Hattori, R.; et al. Efficacy of docetaxel in castration-resistant prostate cancer patients with intraductal carcinoma of the prostate. *Int. J. Clin. Oncol.* **2018**, *23*, 584–590. [[CrossRef](#)]
59. Yamamoto, A.; Kato, M.; Hattori, K.; Naito, Y.; Tochigi, K.; Sano, T.; Kawanishi, H.; Ishikawa, T.; Yuba, T.; Hattori, R.; et al. Propensity score-matched comparison of docetaxel and androgen receptor axis-targeted agents in patients with castration-resistant intraductal carcinoma of the prostate. *BJU Int.* **2020**, *125*, 702–708. [[CrossRef](#)]
60. Cohen, R.J.; McNeal, J.E.; Baillie, T. Patterns of differentiation and proliferation in intraductal carcinoma of the prostate: Significance for cancer progression. *Prostate* **2000**, *43*, 11–19. [[CrossRef](#)]
61. Guo, C.C.; Epstein, J.I. Intraductal carcinoma of the prostate on needle biopsy: Histologic features and clinical significance. *Mod. Pathol.* **2006**, *19*, 1528–1535. [[CrossRef](#)] [[PubMed](#)]
62. Grypari, I.M.; Logotheti, S.; Lazaris, A.C.; Kallidonis, P.; Fokaefs, E.; Melachrinou, M.; Zolota, V.; Tzelepi, V. Isolated Intraductal Carcinoma of the Prostate in Prostatectomy Specimens: Report of 2 Cases and Review of the Literature. *Int. J. Surg. Pathol.* **2020**, *28*, 918–924. [[CrossRef](#)] [[PubMed](#)]
63. Khani, F.; Wobker, S.E.; Hicks, J.L.; Robinson, B.D.; Barbieri, C.E.; De Marzo, A.M.; Epstein, J.I.; Pritchard, C.C.; Lotan, T.L. 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. [[CrossRef](#)]
64. Schweizer, M.T.; Antonarakis, E.S.; Bismar, T.A.; Guedes, L.B.; Cheng, H.H.; Tretiakova, M.S.; Vakar-Lopez, F.; Klemfuss, N.; Konnick, E.Q.; Mostaghel, E.A.; et al. Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations. *JCO Precis. Oncol.* **2019**, *3*, 1–9. [[CrossRef](#)] [[PubMed](#)]
65. Miyai, K.; Divatia, M.K.; Shen, S.S.; Miles, B.J.; Ayala, A.G.; Ro, J.Y. 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*, 1572–1581. [[CrossRef](#)]
66. Lotan, T.L.; Gumuskaya, B.; Rahimi, H.; Hicks, J.L.; Iwata, T.; Robinson, B.D.; Epstein, J.I.; De Marzo, A.M. Cytoplasmic PTEN protein loss distinguishes intraductal carcinoma of the prostate from high-grade prostatic intraepithelial neoplasia. *Mod. Pathol.* **2013**, *26*, 587–603. [[CrossRef](#)]

67. Morais, C.L.; Han, J.S.; Gordetsky, J.; Nagar, M.S.; Anderson, A.E.; Lee, S.; Hicks, J.L.; Zhou, M.; Magi-Galluzzi, C.; Shah, R.B.; 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*, 169–178. [[CrossRef](#)]
68. Shah, R.B.; Yoon, J.; Liu, G.; Tian, W. 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. [[CrossRef](#)] [[PubMed](#)]
69. Hickman, R.A.; Yu, H.; Li, J.; Kong, M.; Shah, R.B.; Zhou, M.; Melamed, J.; Deng, F.M. Atypical Intraductal Cribriform Proliferations of the Prostate Exhibit Similar Molecular and Clinicopathologic Characteristics as Intraductal Carcinoma of the Prostate. *Am. J. Surg. Pathol.* **2017**, *41*, 550–556. [[CrossRef](#)]
70. Haffner, M.C.; Weier, C.; Xu, M.M.; Vaghasia, A.; Gurel, B.; Gumuskaya, B.; Esopi, D.M.; Fedor, H.; Tan, H.L.; Kulac, I.; 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. [[CrossRef](#)]
71. Mosquera, J.M.; Perner, S.; Demichelis, F.; Kim, R.; Hofer, M.D.; Mertz, K.D.; Paris, P.L.; Simko, J.; Collins, C.; Bismar, T.A.; et al. Morphological features of TMPRSS2-ERG gene fusion prostate cancer. *J. Pathol.* **2007**, *212*, 91–101. [[CrossRef](#)] [[PubMed](#)]
72. Han, B.; Suleman, K.; Wang, L.; Siddiqui, J.; Sercia, L.; Magi-Galluzzi, C.; Palanisamy, N.; Chinnaiyan, A.M.; Zhou, M.; Shah, R.B. 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*, 478–485. [[CrossRef](#)] [[PubMed](#)]
73. Bettendorf, O.; Schmidt, H.; Staebler, A.; Grobholz, R.; Heinecke, A.; Boecker, W.; Hertle, L.; Semjonow, A. 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*, 565–572. [[CrossRef](#)] [[PubMed](#)]
74. Downes, M.R.; Satturwar, S.; Trudel, D.; van der Kwast, T.H. Evaluation of ERG and PTEN protein expression in cribriform architecture prostate carcinomas. *Pathol. Res. Pract.* **2017**, *213*, 34–38. [[CrossRef](#)]
75. Schneider, T.M.; Osunkoya, A.O. ERG expression in intraductal carcinoma of the prostate: Comparison with adjacent invasive prostatic adenocarcinoma. *Mod. Pathol.* **2014**, *27*, 1174–1178. [[CrossRef](#)] [[PubMed](#)]
76. Nie, L.; Pan, X.; Zhang, M.; Yin, X.; Gong, J.; Chen, X.; Xu, M.; Zhou, Q.; Chen, N. The expression profile and heterogeneity analysis of ERG in 633 consecutive prostate cancers from a single center. *Prostate* **2019**, *79*, 819–825. [[CrossRef](#)] [[PubMed](#)]
77. Torabi-Nezhad, S.; Malekmakan, L.; Mashayekhi, M.; Daneshian, A. Histopathological features of intra-ductal carcinoma of prostatic and high grade prostatic intraepithelialneoplasia and correlation with PTEN and P63. *Prostate* **2016**, *76*, 394–401. [[CrossRef](#)]
78. Shah, R.B.; Shore, K.T.; Yoon, J.; Mendrinos, S.; McKenney, J.K.; Tian, W. PTEN loss in prostatic adenocarcinoma correlates with specific adverse histologic features (intraductal carcinoma, cribriform Gleason pattern 4 and stromogenic carcinoma). *Prostate* **2019**, *79*, 1267–1273. [[CrossRef](#)] [[PubMed](#)]
79. Dawkins, H.J.; Sellner, L.N.; Turbett, G.R.; Thompson, C.A.; Redmond, S.L.; McNeal, J.E.; Cohen, R.J. 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*, 265–270. [[CrossRef](#)]
80. Grosset, A.A.; Dallaire, F.; Nguyen, T.; Birlea, M.; Wong, J.; Daoust, F.; Roy, N.; Kougioumoutzakakis, A.; Azzi, F.; Aubertin, K.; et al. Identification of intraductal carcinoma of the prostate on tissue specimens using Raman micro-spectroscopy: A diagnostic accuracy case-control study with multicohort validation. *PLoS Med.* **2020**, *17*, e1003281. [[CrossRef](#)]
81. Ramaswamy, S.; Nakamura, N.; Vazquez, F.; Batt, D.B.; Perera, S.; Roberts, T.M.; Sellers, W.R. Regulation of G1 progression by the PTEN tumor suppressor protein is linked to inhibition of the phosphatidylinositol 3-kinase/Akt pathway. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 2110–2115. [[CrossRef](#)] [[PubMed](#)]
82. Cairns, P.; Okami, K.; Halachmi, S.; Halachmi, N.; Esteller, M.; Herman, J.G.; Jen, J.; Isaacs, W.B.; Bova, G.S.; Sidransky, D. Frequent inactivation of PTEN/MMAC1 in primary prostate cancer. *Cancer Res.* **1997**, *57*, 4997–5000. [[PubMed](#)]
83. Suzuki, H.; Freije, D.; Nusskern, D.R.; Okami, K.; Cairns, P.; Sidransky, D.; Isaacs, W.B.; Bova, G.S. Interfocal heterogeneity of PTEN/MMAC1 gene alterations in multiple metastatic prostate cancer tissues. *Cancer Res.* **1998**, *58*, 204–209. [[PubMed](#)]
84. Jamaspishvili, T.; Berman, D.M.; Ross, A.E.; Scher, H.I.; De Marzo, A.M.; Squire, J.A.; Lotan, T.L. Clinical implications of PTEN loss in prostate cancer. *Nat. Rev. Urol.* **2018**, *15*, 222–234. [[CrossRef](#)]
85. Lotan, T.L.; Gurel, B.; Sutcliffe, S.; Esopi, D.; Liu, W.; Xu, J.; Hicks, J.L.; Park, B.H.; Humphreys, E.; Partin, A.W.; 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*, 6563–6573. [[CrossRef](#)]
86. Ahearn, T.U.; Pettersson, A.; Ebot, E.M.; Gerke, T.; Graff, R.E.; Morais, C.L.; Hicks, J.L.; Wilson, K.M.; Rider, J.R.; Sesso, H.D.; et al. A Prospective Investigation of PTEN Loss and ERG Expression in Lethal Prostate Cancer. *J. Natl. Cancer Inst.* **2016**, *108*. [[CrossRef](#)]
87. Hamid, A.A.; Gray, K.P.; Huang, Y.; Bowden, M.; Pomerantz, M.; Loda, M.; Sweeney, C.J. Loss of PTEN Expression Detected by Fluorescence Immunohistochemistry Predicts Lethal Prostate Cancer in Men Treated with Prostatectomy. *Eur. Urol. Oncol.* **2019**, *2*, 475–482. [[CrossRef](#)]
88. Choucair, K.; Ejdelman, J.; Brimo, F.; Aprikian, A.; Chevalier, S.; Lapointe, J. PTEN genomic deletion predicts prostate cancer recurrence and is associated with low AR expression and transcriptional activity. *BMC Cancer* **2012**, *12*, 543. [[CrossRef](#)]
89. Wang, X.; Jiang, X. Post-translational regulation of PTEN. *Oncogene* **2008**, *27*, 5454–5463. [[CrossRef](#)]

90. Tomlins, S.A.; Rhodes, D.R.; Perner, S.; Dhanasekaran, S.M.; Mehra, R.; Sun, X.W.; Varambally, S.; Cao, X.; Tchinda, J.; Kuefer, R.; et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science* **2005**, *310*, 644–648. [[CrossRef](#)]
91. Gasparrini, S.; Cimadamore, A.; Mazzucchelli, R.; Scarpelli, M.; Massari, F.; Raspollini, M.R.; Galosi, A.B.; Lopez-Beltran, A.; Cheng, L.; Montironi, R. Pathology and molecular updates in tumors of the prostate: Towards a personalized approach. *Expert Rev. Mol. Diagn* **2017**, *17*, 781–789. [[CrossRef](#)] [[PubMed](#)]
92. Lokman, U.; Erickson, A.M.; Vasarainen, H.; Rannikko, A.S.; Mirtti, T. PTEN Loss but Not ERG Expression in Diagnostic Biopsies Is Associated with Increased Risk of Progression and Adverse Surgical Findings in Men with Prostate Cancer on Active Surveillance. *Eur. Urol. Focus* **2017**, *4*, 867–873. [[CrossRef](#)] [[PubMed](#)]
93. Deramandt, T.B.; Remy, P.; Stiegler, P. Identification of interaction partners for two closely-related members of the ETS protein family, FLI and ERG. *Gene* **2001**, *274*, 169–177. [[CrossRef](#)]
94. Hägglöf, C.; Hammarsten, P.; Strömvall, K.; Egevad, L.; Josefsson, A.; Stattin, P.; Granfors, T.; Bergh, A. TMPRSS2-ERG expression predicts prostate cancer survival and associates with stromal biomarkers. *PLoS ONE* **2014**, *9*, e86824. [[CrossRef](#)] [[PubMed](#)]
95. Gao, X.; Li, L.Y.; Zhou, F.J.; Xie, K.J.; Shao, C.K.; Su, Z.L.; Sun, Q.P.; Chen, M.K.; Pang, J.; Zhou, X.F.; et al. ERG rearrangement for predicting subsequent cancer diagnosis in high-grade prostatic intraepithelial neoplasia and lymph node metastasis. *Clin. Cancer Res.* **2012**, *18*, 4163–4172. [[CrossRef](#)]
96. Hoogland, A.M.; Jenster, G.; van Weerden, W.M.; Trapman, J.; van der Kwast, T.; Roobol, M.J.; Schroder, F.H.; Wildhagen, M.F.; van Leenders, G.J. ERG immunohistochemistry is not predictive for PSA recurrence, local recurrence or overall survival after radical prostatectomy for prostate cancer. *Mod. Pathol.* **2012**, *25*, 471–479. [[CrossRef](#)]
97. Kron, K.; Liu, L.; Trudel, D.; Pethe, V.; Trachtenberg, J.; Fleshner, N.; Bapat, B.; van der Kwast, T. Correlation of ERG expression and DNA methylation biomarkers with adverse clinicopathologic features of prostate cancer. *Clin. Cancer Res.* **2012**, *18*, 2896–2904. [[CrossRef](#)]
98. Attard, G.; Clark, J.; Ambroisine, L.; Fisher, G.; Kovacs, G.; Flohr, P.; Berney, D.; Foster, C.S.; Fletcher, A.; Gerald, W.L.; et al. Duplication of the fusion of TMPRSS2 to ERG sequences identifies fatal human prostate cancer. *Oncogene* **2008**, *27*, 253–263. [[CrossRef](#)]
99. Latour, M.; Amin, M.B.; Billis, A.; Egevad, L.; Grignon, D.J.; Humphrey, P.A.; Reuter, V.E.; Sakr, W.A.; Srigley, J.R.; Wheeler, T.M.; et al. Grading of invasive cribriform carcinoma on prostate needle biopsy: An interobserver study among experts in genitourinary pathology. *Am. J. Surg. Pathol.* **2008**, *32*, 1532–1539. [[CrossRef](#)]
100. Jermyn, M.; Desroches, J.; Aubertin, K.; St-Arnaud, K.; Madore, W.J.; De Montigny, E.; Guiot, M.C.; Trudel, D.; Wilson, B.C.; Petrecca, K.; et al. A review of Raman spectroscopy advances with an emphasis on clinical translation challenges in oncology. *Phys. Med. Biol.* **2016**, *61*, R370–r400. [[CrossRef](#)]
101. Jermyn, M.; Desroches, J.; Mercier, J.; St-Arnaud, K.; Guiot, M.C.; Leblond, F.; Petrecca, K. Raman spectroscopy detects distant invasive brain cancer cells centimeters beyond MRI capability in humans. *Biomed. Opt. Express* **2016**, *7*, 5129–5137. [[CrossRef](#)]
102. Jermyn, M.; Desroches, J.; Mercier, J.; Tremblay, M.A.; St-Arnaud, K.; Guiot, M.C.; Petrecca, K.; Leblond, F. Neural networks improve brain cancer detection with Raman spectroscopy in the presence of operating room light artifacts. *J. Biomed. Opt.* **2016**, *21*, 94002. [[CrossRef](#)]
103. Jermyn, M.; Mok, K.; Mercier, J.; Desroches, J.; Pichette, J.; Saint-Arnaud, K.; Bernstein, L.; Guiot, M.C.; Petrecca, K.; Leblond, F. Intraoperative brain cancer detection with Raman spectroscopy in humans. *Sci. Transl. Med.* **2015**, *7*, 274ra219. [[CrossRef](#)]
104. Aubertin, K.; Trinh, V.Q.; Jermyn, M.; Baksic, P.; Grosset, A.A.; Desroches, J.; St-Arnaud, K.; Birlea, M.; Vladoiu, M.C.; Latour, M.; et al. Mesoscopic characterization of prostate cancer using Raman spectroscopy: Potential for diagnostics and therapeutics. *BJU Int.* **2018**, *122*, 326–336. [[CrossRef](#)]
105. Pinto, M.; Zorn, K.; Tremblay, J.P.; Desroches, J.; Aubertin, K.; Marple, E.; Kent, K.; Leblond, F.; Trudel, D.; Lesage, F. Integration of a Raman spectroscopy system to a robotic-assisted surgical system for real time tissue characterization during radical prostatectomy procedures. *J. Biomed. Opt.* **2019**, *24*, 1–10. [[CrossRef](#)] [[PubMed](#)]
106. Plante, A.; Dallaire, F.; Grosset, A.A.; Nguyen, T.; Birlea, M.; Wong, J.; Daoust, F.; Roy, N.; Kougioumoutzakis, A.; Azzi, F.; et al. Dimensional reduction based on peak fitting of Raman micro spectroscopy data improves detection of prostate cancer in tissue specimens. *J. Biomed. Opt.* **2021**, *26*, 116501. [[CrossRef](#)] [[PubMed](#)]
107. Bottcher, R.; Kweldam, C.F.; Livingstone, J.; Lalonde, E.; Yamaguchi, T.N.; Huang, V.; Yousif, F.; Fraser, M.; Bristow, R.G.; van der Kwast, T.; et al. Cribriform and intraductal prostate cancer are associated with increased genomic instability and distinct genomic alterations. *BMC Cancer* **2018**, *18*, 8. [[CrossRef](#)] [[PubMed](#)]
108. Salles, D.C.; Vidotto, T.; Faisal, F.A.; Tosoian, J.J.; Guedes, L.B.; Muranyi, A.; Bai, I.; Singh, S.; Yan, D.; Shanmugam, K.; et al. Assessment of MYC/PTEN Status by Gene-Protein Assay in Grade Group 2 Prostate Biopsies. *J. Mol. Diagn.* **2021**, *23*, 1030–1041. [[CrossRef](#)]
109. Olkhov-Mitsel, E.; Siadat, F.; Kron, K.; Liu, L.; Savio, A.J.; Trachtenberg, J.; Fleshner, N.; van der Kwast, T.; Bapat, B. Distinct DNA methylation alterations are associated with cribriform architecture and intraductal carcinoma in Gleason pattern 4 prostate tumors. *Oncol. Lett.* **2017**, *14*, 390–396. [[CrossRef](#)] [[PubMed](#)]
110. Zhao, J.; Sun, G.; Zhu, S.; Dai, J.; Chen, J.; Zhang, M.; Ni, Y.; Zhang, H.; Shen, P.; Zhao, X.; et al. Circulating tumour DNA reveals genetic traits of patients with intraductal carcinoma of the prostate. *BJU Int.* **2021**. [[CrossRef](#)]

111. Lee, S.; Han, J.S.; Chang, A.; Ross, H.M.; Montironi, R.; Yorukoglu, K.; Lane, Z.; Epstein, J.I. Small cell-like change in prostatic intraepithelial neoplasia, intraductal carcinoma, and invasive prostatic carcinoma: A study of 7 cases. *Hum. Pathol.* **2013**, *44*, 427–431. [[CrossRef](#)] [[PubMed](#)]
112. Sarsik, B.; Karadeniz, N.; Simsir, A.; Akyol, R.; Yorukoglu, K.; Sen, S. Acinar Adenocarcinoma of Prostate with Predominant Ttf-1 Positive Intraductal Component. *Turk. Patoloji Derg.* **2017**, *33*, 70–73. [[CrossRef](#)] [[PubMed](#)]
113. Castro, E.; Goh, C.; Leongamornlert, D.; Saunders, E.; Tymrakiewicz, M.; Dadaev, T.; Govindasami, K.; Guy, M.; Ellis, S.; Frost, D.; et al. Effect of BRCA Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer. *Eur. Urol.* **2015**, *68*, 186–193. [[CrossRef](#)]
114. Willems, A.J.; Dawson, S.J.; Samaratunga, H.; De Luca, A.; Antill, Y.C.; Hopper, J.L.; Thorne, H.J. Loss of heterozygosity at the BRCA2 locus detected by multiplex ligation-dependent probe amplification is common in prostate cancers from men with a germline BRCA2 mutation. *Clin. Cancer Res.* **2008**, *14*, 2953–2961. [[CrossRef](#)]
115. Akbari, M.R.; Wallis, C.J.; Toi, A.; Trachtenberg, J.; Sun, P.; Narod, S.A.; Nam, R.K. The impact of a BRCA2 mutation on mortality from screen-detected prostate cancer. *Br. J. Cancer* **2014**, *111*, 1238–1240. [[CrossRef](#)] [[PubMed](#)]
116. Castro, E.; Goh, C.; Olmos, D.; Saunders, E.; Leongamornlert, D.; Tymrakiewicz, M.; Mahmud, N.; Dadaev, T.; Govindasami, K.; Guy, M.; et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J. Clin. Oncol.* **2013**, *31*, 1748–1757. [[CrossRef](#)]
117. Murphy, D.G.; Risbridger, G.P.; Bristow, R.G.; Sandhu, S. The Evolving Narrative of DNA Repair Gene Defects: Distinguishing Indolent from Lethal Prostate Cancer. *Eur. Urol.* **2017**, *71*, 748–749. [[CrossRef](#)]
118. Mateo, J.; Carreira, S.; Sandhu, S.; Miranda, S.; Mossop, H.; Perez-Lopez, R.; Nava Rodrigues, D.; Robinson, D.; Omlin, A.; Tunariu, N.; et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N. Engl. J. Med.* **2015**, *373*, 1697–1708. [[CrossRef](#)]
119. Mateo, J.; Porta, N.; Bianchini, D.; McGovern, U.; Elliott, T.; Jones, R.; Syndikus, I.; Ralph, C.; Jain, S.; Varughese, M.; et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): A multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* **2020**, *21*, 162–174. [[CrossRef](#)]
120. Schaeffer, E.; Srinivas, S.; Antonarakis, E.S.; Armstrong, A.J.; Bekelman, J.E.; Cheng, H.; D’Amico, A.V.; Davis, B.J.; Desai, N.; Dorff, T.; et al. NCCN Guidelines Insights: Prostate Cancer, Version 1.2021. *J. Natl. Compr. Canc. Netw.* **2021**, *19*, 134–143. [[CrossRef](#)]
121. Risbridger, G.P.; Taylor, R.A.; Clouston, D.; Sliwinski, A.; Thorne, H.; Hunter, S.; Li, J.; Mitchell, G.; Murphy, D.; Frydenberg, M.; 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. [[CrossRef](#)] [[PubMed](#)]
122. Taylor, R.A.; Fraser, M.; Livingstone, J.; Espiritu, S.M.; Thorne, H.; Huang, V.; Lo, W.; Shiah, Y.J.; Yamaguchi, T.N.; Sliwinski, A.; et al. Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. *Nat. Commun.* **2017**, *8*, 13671. [[CrossRef](#)]
123. Isaacsson Velho, P.; Silberstein, J.L.; Markowski, M.C.; Luo, J.; Lotan, T.L.; Isaacs, W.B.; Antonarakis, E.S. Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. *Prostate* **2018**, *78*, 401–407. [[CrossRef](#)]
124. Antonarakis, E.S.; Shaikat, F.; Isaacsson Velho, P.; Kaur, H.; Shenderov, E.; Pardoll, D.M.; Lotan, T.L. Clinical Features and Therapeutic Outcomes in Men with Advanced Prostate Cancer and DNA Mismatch Repair Gene Mutations. *Eur. Urol.* **2019**, *75*, 378–382. [[CrossRef](#)]
125. Lozano, R.; Salles, D.C.; Sandhu, S.; Aragon, I.M.; Thorne, H.; Lopez-Campos, F.; Rubio-Briones, J.; Gutierrez-Pecharroman, A.M.; Maldonado, L.; di Domenico, T.; et al. Association between BRCA2 alterations and intraductal and cribriform histologies in prostate cancer. *Eur. J. Cancer* **2021**, *147*, 74–83. [[CrossRef](#)]
126. Uysal-Onganer, P.; Kawano, Y.; Caro, M.; Walker, M.M.; Diez, S.; Darrington, R.S.; Waxman, J.; Kypta, R.M. Wnt-11 promotes neuroendocrine-like differentiation, survival and migration of prostate cancer cells. *Mol. Cancer* **2010**, *9*, 55. [[CrossRef](#)] [[PubMed](#)]
127. Shaikhibrahim, Z.; Offermann, A.; Braun, M.; Menon, R.; Syring, I.; Nowak, M.; Halbach, R.; Vogel, W.; Ruiz, C.; Zellweger, T.; et al. MED12 overexpression is a frequent event in castration-resistant prostate cancer. *Endocr. Relat. Cancer* **2014**, *21*, 663–675. [[CrossRef](#)] [[PubMed](#)]
128. Bhandari, V.; Hoey, C.; Liu, L.Y.; Lalonde, E.; Ray, J.; Livingstone, J.; Lesurf, R.; Shiah, Y.J.; Vujcic, T.; Huang, X.; et al. Molecular landmarks of tumor hypoxia across cancer types. *Nat. Genet.* **2019**, *51*, 308–318. [[CrossRef](#)]
129. Chen, S.; Huang, V.; Xu, X.; Livingstone, J.; Soares, F.; Jeon, J.; Zeng, Y.; Hua, J.T.; Petricca, J.; Guo, H.; et al. Widespread and Functional RNA Circularization in Localized Prostate Cancer. *Cell* **2019**, *176*, 831–843. [[CrossRef](#)]
130. Spieker, A.J.; Gordetsky, J.B.; Maris, A.S.; Dehan, L.M.; Denney, J.E.; Arnold Egloff, S.A.; Scarpato, K.; Barocas, D.A.; Giannico, G.A. PTEN expression and morphological patterns in prostatic adenocarcinoma. *Histopathology* **2021**, *79*, 1061–1071. [[CrossRef](#)]
131. Prensner, J.R.; Iyer, M.K.; Sahu, A.; Asangani, I.A.; Cao, Q.; Patel, L.; Vergara, I.A.; Davicioni, E.; Erho, N.; Ghadessi, M.; et al. The long noncoding RNA SCHLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. *Nat. Genet.* **2013**, *45*, 1392–1398. [[CrossRef](#)] [[PubMed](#)]

132. Kidd, S.G.; Carm, K.T.; Bogaard, M.; Olsen, L.G.; Bakken, A.C.; Løvf, M.; Lothe, R.A.; Axcrona, K.; Axcrona, U.; Skotheim, R.I. High expression of SCHLAP1 in primary prostate cancer is an independent predictor of biochemical recurrence, despite substantial heterogeneity. *Neoplasia* **2021**, *23*, 634–641. [[CrossRef](#)]
133. Greenland, N.Y.; Zhang, L.; Cowan, J.E.; Carroll, P.R.; Stohr, B.A.; Simko, J.P. Correlation of a Commercial Genomic Risk Classifier with Histological Patterns in Prostate Cancer. *J. Urol.* **2019**, *202*, 90–95. [[CrossRef](#)] [[PubMed](#)]
134. Taylor, A.S.; Morgan, T.M.; Wallington, D.G.; Chinnaiyan, A.M.; Spratt, D.E.; Mehra, R. Correlation between cribriform/intraductal prostatic adenocarcinoma and percent Gleason pattern 4 to a 22-gene genomic classifier. *Prostate* **2020**, *80*, 146–152. [[CrossRef](#)]
135. Klein, E.A.; Cooperberg, M.R.; Magi-Galluzzi, C.; Simko, J.P.; Falzarano, S.M.; Maddala, T.; Chan, J.M.; Li, J.; Cowan, J.E.; Tsiatis, A.C.; et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur. Urol.* **2014**, *66*, 550–560. [[CrossRef](#)] [[PubMed](#)]
136. Cullen, J.; Rosner, I.L.; Brand, T.C.; Zhang, N.; Tsiatis, A.C.; Moncur, J.; Ali, A.; Chen, Y.; Knezevic, D.; Maddala, T.; et al. A Biopsy-based 17-gene Genomic Prostate Score Predicts Recurrence After Radical Prostatectomy and Adverse Surgical Pathology in a Racially Diverse Population of Men with Clinically Low- and Intermediate-risk Prostate Cancer. *Eur. Urol.* **2015**, *68*, 123–131. [[CrossRef](#)] [[PubMed](#)]
137. Van Den Eeden, S.K.; Lu, R.; Zhang, N.; Quesenberry, C.P., Jr.; Shan, J.; Han, J.S.; Tsiatis, A.C.; Leimpeter, A.D.; Lawrence, H.J.; Febbo, P.G.; et al. A Biopsy-based 17-gene Genomic Prostate Score as a Predictor of Metastases and Prostate Cancer Death in Surgically Treated Men with Clinically Localized Disease. *Eur. Urol.* **2018**, *73*, 129–138. [[CrossRef](#)]
138. Covas Moschovas, M.; Chew, C.; Bhat, S.; Sandri, M.; Rogers, T.; Dell’Oglio, P.; Roof, S.; Reddy, S.; Sighinolfi, M.C.; Rocco, B.; et al. Association Between Oncotype DX Genomic Prostate Score and Adverse Tumor Pathology After Radical Prostatectomy. *Eur. Urol. Focus* **2021**. [[CrossRef](#)]
139. Knudsen, B.S.; Kim, H.L.; Erho, N.; Shin, H.; Alshalalfa, M.; Lam, L.L.C.; Tenggara, I.; Chadwich, K.; Van Der Kwast, T.; Fleshner, N.; et al. Application of a Clinical Whole-Transcriptome Assay for Staging and Prognosis of Prostate Cancer Diagnosed in Needle Core Biopsy Specimens. *J. Mol. Diagn.* **2016**, *18*, 395–406. [[CrossRef](#)]
140. Lee, H.J.; Yousefi, K.; Haddad, Z.; Abdollah, F.; Lam, L.L.; Shin, H.; Alshalalfa, M.; Godebu, E.; Wang, S.; Shabaik, A.; et al. Evaluation of a genomic classifier in radical prostatectomy patients with lymph node metastasis. *Res. Rep. Urol.* **2016**, *8*, 77–84. [[CrossRef](#)]
141. Erho, N.; Crisan, A.; Vergara, I.A.; Mitra, A.P.; Ghadessi, M.; Buerki, C.; Bergstrahl, E.J.; Kollmeyer, T.; Fink, S.; Haddad, Z.; et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. *PLoS ONE* **2013**, *8*, e66855. [[CrossRef](#)] [[PubMed](#)]
142. Karnes, R.J.; Bergstrahl, E.J.; Davicioni, E.; Ghadessi, M.; Buerki, C.; Mitra, A.P.; Crisan, A.; Erho, N.; Vergara, I.A.; Lam, L.L.; et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. *J. Urol.* **2013**, *190*, 2047–2053. [[CrossRef](#)] [[PubMed](#)]
143. Den, R.B.; Feng, F.Y.; Showalter, T.N.; Mishra, M.V.; Trabulsi, E.J.; Lallas, C.D.; Gomella, L.G.; Kelly, W.K.; Birbe, R.C.; McCue, P.A.; et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* **2014**, *89*, 1038–1046. [[CrossRef](#)]
144. Klein, E.A.; Yousefi, K.; Haddad, Z.; Choerung, V.; Buerki, C.; Stephenson, A.J.; Li, J.; Kattan, M.W.; Magi-Galluzzi, C.; Davicioni, E. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. *Eur. Urol.* **2015**, *67*, 778–786. [[CrossRef](#)]
145. Den, R.B.; Yousefi, K.; Trabulsi, E.J.; Abdollah, F.; Choerung, V.; Feng, F.Y.; Dicker, A.P.; Lallas, C.D.; Gomella, L.G.; Davicioni, E.; et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. *J. Clin. Oncol.* **2015**, *33*, 944–951. [[CrossRef](#)]
146. Ross, A.E.; Johnson, M.H.; Yousefi, K.; Davicioni, E.; Netto, G.J.; Marchionni, L.; Fedor, H.L.; Glavaris, S.; Choerung, V.; Buerki, C.; et al. Tissue-based Genomics Augments Post-prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men. *Eur. Urol.* **2016**, *69*, 157–165. [[CrossRef](#)] [[PubMed](#)]
147. Glass, A.G.; Leo, M.C.; Haddad, Z.; Yousefi, K.; du Plessis, M.; Chen, C.; Choerung, V.; Abdollah, F.; Robbins, B.; Ra, S.; et al. Validation of a Genomic Classifier for Predicting Post-Prostatectomy Recurrence in a Community Based Health Care Setting. *J. Urol.* **2016**, *195*, 1748–1753. [[CrossRef](#)] [[PubMed](#)]
148. Freedland, S.J.; Choerung, V.; Howard, L.; De Hoedt, A.; du Plessis, M.; Yousefi, K.; Lam, L.L.; Buerki, C.; Ra, S.; Robbins, B.; et al. Utilization of a Genomic Classifier for Prediction of Metastasis Following Salvage Radiation Therapy after Radical Prostatectomy. *Eur. Urol.* **2016**, *70*, 588–596. [[CrossRef](#)]
149. Klein, E.A.; Haddad, Z.; Yousefi, K.; Lam, L.L.; Wang, Q.; Choerung, V.; Palmer-Aronsten, B.; Buerki, C.; Davicioni, E.; Li, J.; et al. Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk. *Urology* **2016**, *90*, 148–152. [[CrossRef](#)]
150. Nguyen, P.L.; Martin, N.E.; Choerung, V.; Palmer-Aronsten, B.; Kolisnik, T.; Beard, C.J.; Orto, P.F.; Nezoslosky, M.D.; Chen, Y.W.; Shin, H.; et al. Utilization of biopsy-based genomic classifier to predict distant metastasis after definitive radiation and short-course ADT for intermediate and high-risk prostate cancer. *Prostate Cancer Prostatic Dis.* **2017**, *20*, 186–192. [[CrossRef](#)]
151. Spratt, D.E.; Yousefi, K.; Deheshi, S.; Ross, A.E.; Den, R.B.; Schaeffer, E.M.; Trock, B.J.; Zhang, J.; Glass, A.G.; Dicker, A.P.; et al. Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease. *J. Clin. Oncol.* **2017**, *35*, 1991–1998. [[CrossRef](#)]

152. Van den Broeck, T.; Moris, L.; Gevaert, T.; Tosco, L.; Smeets, E.; Fishbane, N.; Liu, Y.; Helsen, C.; Margrave, J.; Buerki, C.; et al. Validation of the Decipher Test for Predicting Distant Metastatic Recurrence in Men with High-risk Nonmetastatic Prostate Cancer 10 Years After Surgery. *Eur. Urol. Oncol.* **2019**, *2*, 589–596. [[CrossRef](#)]
153. Cooperberg, M.R.; Davicioni, E.; Crisan, A.; Jenkins, R.B.; Ghadessi, M.; Karnes, R.J. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. *Eur. Urol.* **2015**, *67*, 326–333. [[CrossRef](#)]
154. Badani, K.; Thompson, D.J.; Buerki, C.; Davicioni, E.; Garrison, J.; Ghadessi, M.; Mitra, A.P.; Wood, P.J.; Hornberger, J. Impact of a genomic classifier of metastatic risk on postoperative treatment recommendations for prostate cancer patients: A report from the DECIDE study group. *Oncotarget* **2013**, *4*, 600–609. [[CrossRef](#)]
155. Badani, K.K.; Kemeter, M.J.; Febbo, P.G.; Lawrence, H.J.; Denes, B.S.; Rothney, M.P.; Rothberg, M.B.; Brown, G.A. The Impact of a Biopsy Based 17-Gene Genomic Prostate Score on Treatment Recommendations in Men with Newly Diagnosed Clinically Prostate Cancer Who are Candidates for Active Surveillance. *Urol. Pract.* **2015**, *2*, 181–189. [[CrossRef](#)]
156. Michalopoulos, S.N.; Kella, N.; Payne, R.; Yohannes, P.; Singh, A.; Hettinger, C.; Yousefi, K.; Hornberger, J. Influence of a genomic classifier on post-operative treatment decisions in high-risk prostate cancer patients: Results from the PRO-ACT study. *Curr. Med. Res. Opin.* **2014**, *30*, 1547–1556. [[CrossRef](#)]
157. Nguyen, P.L.; Shin, H.; Yousefi, K.; Thompson, D.J.; Hornberger, J.; Hyatt, A.S.; Badani, K.K.; Morgan, T.M.; Feng, F.Y. Impact of a Genomic Classifier of Metastatic Risk on Postprostatectomy Treatment Recommendations by Radiation Oncologists and Urologists. *Urology* **2015**, *86*, 35–40. [[CrossRef](#)] [[PubMed](#)]
158. Gore, J.L.; du Plessis, M.; Santiago-Jiménez, M.; Yousefi, K.; Thompson, D.J.S.; Karsh, L.; Lane, B.R.; Franks, M.; Chen, D.Y.T.; Bandyk, M.; et al. Decipher test impacts decision making among patients considering adjuvant and salvage treatment after radical prostatectomy: Interim results from the Multicenter Prospective PRO-IMPACT study. *Cancer* **2017**, *123*, 2850–2859. [[CrossRef](#)]
159. Vince, R.A., Jr.; Jiang, R.; Qi, J.; Tosoian, J.J.; Takele, R.; Feng, F.Y.; Linsell, S.; Johnson, A.; Shetty, S.; Hurley, P.; et al. Impact of Decipher Biopsy testing on clinical outcomes in localized prostate cancer in a prospective statewide collaborative. *Prostate Cancer Prostatic Dis.* **2021**. [[CrossRef](#)] [[PubMed](#)]
160. Smith, S.C.; Gandhi, J.S.; Moch, H.; Aron, M.; Comperat, E.; Paner, G.P.; McKenney, J.K.; Amin, M.B. Similarities and Differences in the 2019 ISUP and GUPS Recommendations on Prostate Cancer Grading: A Guide for Practicing Pathologists. *Adv. Anat. Pathol.* **2021**, *28*, 1–7. [[CrossRef](#)]
161. van Leenders, G.; van der Kwast, T.H.; Grignon, D.J.; Evans, A.J.; Kristiansen, G.; Kweldam, C.F.; Litjens, G.; McKenney, J.K.; Melamed, J.; Mottet, N.; et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. *Am. J. Surg. Pathol.* **2020**, *44*, e87–e99. [[CrossRef](#)] [[PubMed](#)]