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Research Article

Intraductal carcinoma of the prostate in an Irish prostate cancer patient cohort—an aggressive pathology and a strong familial link

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ABSTRACT

Background: The prevalence of intraductal carcinoma of the prostate (IDC-P) is poorly studied in the Irish population. This study investigated the incidence and clinicopathologic characteristics of IDC-P in an Irish prostate cancer (PCa) patient cohort. The study also discusses the rationale for genetic counseling and screening in Irish patients with familial risk factors for IDC-P.

Materials and methods: This study investigated patients diagnosed with IDC-P on prostate biopsy from 2012 to 2016. Primary outcome measurements were incidence, management, and clinical outcomes after follow-up in patients with IDC-P. The secondary outcome measurement was to identify a familial link for IDC-P.

Results: A total of 1,143 patients were diagnosed with PCa on needle biopsy, of which 30 (2.3%) had concomitant IDC-P. Mean age and prostate-specific antigen at diagnosis were 68.6 ± 10.5 years (range 53–85 years) and 9.15 ± 8.65 ng/mL (range 2.1–166 ng/mL), respectively. In total, 17 of 30 patients (57%) were diagnosed with concomitant high-grade (i.e., ≥Gleason score 8) PCa. Eight patients (27%) were treated with radical prostatectomy; of which five had biochemical recurrence (BCR) after 10.55 ± 25.9 months. Eleven patients (37%) received radical radiotherapy; of which one had BCR after 36 months. Eleven patients (37%) presented with advanced PCa and were managed with androgen deprivation therapy ± chemotherapy. A family history for PCa in first-degree relatives was found in eight patients (27%).

Conclusions: IDC-P is associated with more aggressive clinicopathologic features and an increased risk of BCR after treatment. In Ireland, clinical guidelines and a genetic screening pathway are required to provide early detection and appropriate multimodal management of patients with IDC-P.

1. Introduction

Intraductal carcinoma of the prostate (IDC-P) is associated with several poor prognostic features such as advanced local stage, extracapsular extension, lymph node metastasis, higher Gleason grade, larger tumor volumes, and accelerated disease progression.[1–4] In IDC-P, malignant cells grow in pre-existing prostatic ducts and acini, and their morphology has high-grade Gleason patterns 4 and 5, with cribriform architecture and comedo necrosis.[5] In patients with germline BRCA2 mutations, IDC-P is independently associated with decreased progression-free and overall survival.[6]

Estimates globally of the prevalence of IDC-P remain poor and under-reported.[6,7] The prevalence of IDC-P is poorly studied in the Irish population and no Irish data are available on the management and clinical outcomes after treatment for IDC-P. Furthermore, there is no established genetic counseling or screening pathway for patients with suspected risk factors (e.g., germline BRCA 2 mutations or microsatellite instability) in suspicious pathologies such as IDC-P. In the present study, the authors investigate the incidence, clinicopathologic characteristics of IDC-P in an Irish prostate cancer (PCa) patient cohort. They also discuss the rationale for genetic counseling and screening in Irish patients with a finding of IDC-P.

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2. Materials and methods

2.1. Overview of study design

A retrospective institutional review board approved study was performed at Beaumont Hospital, Dublin, Ireland, to investigate patients diagnosed with IDC-P. Patients were identified by running a keyword search of "intraductal" on all reported prostate specimens; be it biopsy or prostatectomy specimen. Primary outcome measurements were incidence, management, and clinical outcomes after follow-up in patients with IDC-P. Secondary outcome measurement was to identify a familial link for IDC-P. Patients diagnosed with IDC-P on 12-core transrectal ultrasound–guided prostate biopsy were identified and reviewed over a 5-year period (2012–2016 inclusive) from a prospectively maintained histopathologic database. All prostate specimens were reviewed by a consultant histopathologist and all IDC-P cases were discussed at a weekly uro-oncology multidisciplinary team meeting. IDC-P specimens were reported according to the Guo and Epstein criteria.[5] P63 and 34BE12 immunohistochemical stains were performed when the diagnosis of IDC-P was ambiguous on conventional hematoxylin and eosin histology. Local staging involved multiparametric prostate magnetic resonance imaging (MRI) and a bone scan was indicated if biopsy showed leading Gleason score >4 or prostate-specific antigen (PSA) >20 ng/mL.

2.2. Patient demographics

Clinicopathologic data including age, PSA at diagnosis, clinical stage, treatment strategy (i.e., surgery, radiotherapy, androgen deprivation therapy (ADT), chemotherapy, multimodal treatment), and survival outcomes [biochemical recurrence (BCR) and death] were analyzed. In addition, histopathology of patients undergoing radical retropubic prostatectomy were analyzed for their corresponding pathologic staging.

2.3. Treatment options

Radical surgery involved open, laparoscopic and robot-assisted modalities. External beam radiotherapy (EBRT) consisted of 3D-conformal radiotherapy with a total delivery dose of 74 Gray in 37 fractions delivered five times/wk. When indicated, ADT consisted of 3 years of an LHRH (luteinizing hormone-releasing hormone) analogue in combination with radiation therapy. Familial link for PCa was established via a phone interview with the patient or next of kin in cases of patient death. Data are presented as a median ± standard deviation.

3. Results

3.1. Patient demographics

Between 2012 and 2016, 2,669 patients underwent transrectal ultrasound-guided prostate biopsies and 1,143 patients (43%) were diagnosed with PCa. In total, 30 of 1,143 patients (2.3%) were diagnosed with concomitant IDC-P. The mean age was 68.6 ± 10.5 years (range 53–85 years) and mean PSA at diagnosis was 9.15 ± 8.65 ng/mL (range 2.1–166 ng/mL).

3.2. Clinicopathologic features

IDC-P was associated with invasive adenocarcinoma of the prostate in all cases. Clinical staging with digital rectal examination demonstrated ≥cT2 in 21 of 30 patients (70%) (Table 1). The International Society of Urological Pathology (ISUP) grade groups (GGs) of concomitant invasive PCa was GG 1 (Gleason 3 + 3) in three cases (11%), GG 2 (Gleason 3 + 4) in three cases (11%), GG 3 (Gleason 4 + 3) in seven cases (22%), GG 4 (Gleason 4 + 4) in 10 cases (34%) and GG 5 (Gleason 4 + 5) in seven cases (22%). Radiologic staging with MRI and conventional bone scan with technetium-99 radiolabeled isotope demonstrated organ-confined disease (T2) in 11 patients (35%), locally advanced (T3) in 12 patients (39%) and four patients (13%) had invasion into adjacent organs (T4). Local staging with MRI was performed in 26 of 30 patients (87%) and omitted in four patients (13%) because of incompatible pacemakers ($n = 2$) or the presentation of advanced metastatic disease ($n = 2$). Bone metastases were present in 10 patients (33%) at presentation.

3.3. Treatment

3.3.1. Surgery

Eight patients (27%) underwent radical prostatectomy (RP). The clinicopathologic findings are summarized in Table 2. Mean age was 67 years and PSA was 6.15 ng/mL. Mean tumor volume was 18.25% (range 5–40%). Five patients (62.5%) had a BCR (defined as two consecutive PSA rises >0.2 ng/mL postoperatively)[8] after 10.55 ± 25.9 months. Three patients (37%) had local recurrence in the prostate bed and two (25%) had a metastatic pelvic node on imaging. Among patients with BCR, two patients were managed with salvage radiotherapy to the prostate fossa, two patients were commenced on androgen depravation therapy for metastatic disease, and one patient is currently on PSA surveillance.

3.3.2. Radiotherapy

EBRT was delivered to 11 patients (36.5%). PSA at diagnosis, Gleason grade groups and duration of follow-up are demonstrated in Table 3. BCR, defined as a PSA increase of ≥2 ng/mL above the post radiotherapy treatment nadir,[9] was noted in one patient (9%), 36 months after completing EBRT and 6 months after discontinuing ADT. Subsequently, the patient was commenced on docetaxel chemotherapy. At present, four of 11 patients are under close surveillance for PSA levels that are trending upwards.

Table 1
Demographic and clinicopathologic features of patients diagnosed with IDC-P.

Patient demographics	***N* number**	**Range/Percentage**
Median Age ± SD (range) (yr)	67.7 ± 10.5	53–85
Stage	**Clinical**	**Radiologic**
T1c	8 (27%)	
T2	11 (35%)	11 (35%)
T3	7 (23%)	12 (39%)
T4	4 (13%)	4 (13%)
Biopsy ISUP Grade Groups (Gleason score)		
GG 1 (3 + 3)	3	11%
GG 2 (3 + 4	3	11%
GG 3 (4 + 3)	7	22%
GG 4 (4 + 4)	10	34%
GG 5 (4 + 5)	7	22%
Treatment modality		
Radical prostatectomy	8	27%
Radical radiotherapy	11	37%
ADT alone	3	10%
ADT & palliative radiotherapy	3	10%
ADT & chemotherapy	5	16%
Mortality	4	13%

ADT, androgen deprivation therapy; GG, ISUP grade group; IDC-P, intraductal carcinoma of the prostate; SD, standard deviation.

Table 2
Clinicopathologic features of patients undergoing Radical Prostatectomy (RP).

N	Age (yr)	PSA (ng/mL)	Clinical T-stage	MRI T-stage	Biopsy GG	RP specimen pathologic features					Recurrence	Adjuvant treatment
						RP GG	Margins	TV (%)	IDC-P	Pathologic T-stage		
1	67	6.2	1c	2	3	2	Negative	5	Present	2c	No	No
2	67	11	2b	2	3	3	Negative	10	Present	2c	Yes	ADT
3	59	3.4	2c	2	4	4	Positive	30	Present	3a	Yes	Salvage radiotherapy
4	67	5.9	2c	2	4	4	Negative	10	Present	2c	Yes	ADT
5	65	6.72	1c	3	3	3	Positive	40	Present	3a	Yes	Salvage radiotherapy
6	61	6.1	1c	2	4	4	Positive	30	Present	3a	No	No
7	68	6.9	1c	2	4	4	Negative	15	Present	2c	Yes	PSA surveillance
8	73	2.5	3a	2	3	3	Negative	5	Present	2c	No	No
Mean	67	6.15										

ADT, androgen deprivation therapy; GG, ISUP grade group; IDC-P, intraductal carcinoma of the prostate; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RP, radical prostatectomy, TV, tumor volume.

3.3.3. *ADT ± palliative radiotherapy*

Eleven patients (36.5%) presented with advanced metastatic disease and were treated with ADT and/or palliative radiotherapy and/or chemotherapy. Their characteristics are summarized in Table 4. There were four PCa-related mortalities (13%) 28 ± 18 months after diagnosis.

3.3.4. *Establishing a familial link*

Telephone interviews were conducted with patients and/or their next of kin. Eight patients (27%) reported at least one first degree relative (FDR) with PCa. Their median age at diagnosis was 61 years (range 53–73 years) and three patients were <60 years. Median PSA was 7.85 ng/mL (range 3.4–36 ng/mL). Biopsy pathology showed IDC-P with concomitant prostate adenocarcinoma as follows: GG 3, $n = 1$ (12.5%); GG 4, $n = 5$ (62.5%), and GG 5, $n = 2$ (25%). Three familial members underwent RP, two received EBRT, and three underwent ADT ± chemotherapy and palliative radiotherapy. One patient also had two FDRs with breast cancer (father and sister), one patient had an FDR with endometrial cancer, and one patient also had a positive family history of PCa in three 1 FDRs in two successive generations (two brothers, father, and grandfather).

4. Discussion

IDC-P is an increasingly recognized pathologic entity that is associated with aggressive high-grade PCa, high-risk disease, and poor survival outcomes.[10] This study investigates the incidence, natural history, management, and outcomes of Irish patients with IDC-P. The study also investigates a familial link of IDC-P among Irish patients. The main findings of this study are that IDC-P is associated with high-grade invasive adenocarcinoma of the prostate and high-risk features, as 52% of cases were extraprostatic stage (T3 or T4 disease) on imaging and 37% of cases were metastatic at diagnosis. Notably, the authors identified a familial link of PCa in 27% of patients ($n = 8$ of 30) and this finding emphasizes a role for availing of genetic screening in Ireland for patients with a finding of IDC-P.

The incidence of IDC-P described herein is 2.3% and this is similar to a series described by Watts et al[11] where IDC-P was diagnosed in 2.8% of 1,176 consecutive prostate biopsies. This relatively low incidence is likely due to under-reporting as pathologic reporting is only a recommended requirement in Ireland since 2017.[12] In pathologic specimens, IDC-P consists of cuboidal columnar intraductal or intra-acinar cells with neoplastic proliferation and preservation of the basal cell layer, usually juxtaposed with invasive adenocarcinoma of the prostate.[10] Prostatic ductal carcinoma differs as this pathologic entity consists of pseudostratified columnar cells without a basal cell lining.[13] In the present series, all IDC-P cases had concomitant invasive adenocarcinoma of the prostate on needle biopsy. There were no cases of isolated IDC-P without invasive adenocarcinoma of the prostate and isolated IDC-P without invasive PCa has been reported as being less than 0.3% in

Table 3
Characteristics of patients undergoing external beam radiotherapy (ERBT).

N	11	
Age (yr)	69 ± 7	
PSA	9 (5.7–30.1)	
GG		
GG 1	2 (18%)	
GG 2	2 (18%)	
GG 3	2 (18%)	
GG 4	2 (18%)	
GG 5	3 (27%)	
Stage	Clinical	Radiological
T1	3 (27%)	
T2	3 (27%)	4 (36%)
T3a	3 (27%)	2 (18%)
T3b		2 (18%)
T4	1 (9%)	1 (9%)
Mean follow-up (d)	1,200 (204–2,738)	
Biochemical recurrence	1 (9%)	
Adjuvant treatment	1 (Docetaxel)	
Mortality	0	

EBRT, external beam radiotherapy; GG, ISUP grade group; PSA, prostate-specific antigen.

Table 4
Characteristics of patients undergoing ADT ± palliative treatment for high-grade locally advanced and metastatic prostate cancer.

N	11
Age (yr)	67.9 ± 10
PSA	23 (2.1–166)
ISUP GG	
GG 1	1 (9%)
GG 2	0
GG 3	2 (18%)
GG 4	3 (27%)
GG 5	5 (45%)
Clinical T-stage	
cT1	2 (18%)
cT2	2 (18%)
cT3	4 (36%)
cT4	3 (27%)
Mean follow-up (d)	900 (120–4,023)
ADT alone	3 (27%)
ADT & palliative radiotherapy	3 (27%)
ADT + palliative radiotherapy + chemotherapy	5 (45%
Mortality	4 (36%)

ADT, androgen deprivation therapy; GG, ISUP grade group; PSA, prostate-specific antigen.

previous studies[5,11,14] and is an indication for repeat biopsy.[12] Similar to the review by Porter et al[10], the authors of this study also show that the prevalence of IDC-P is strongly associated with increasing National Comprehensive Cancer Network risk categories. The authors found the incidence to be 11% for low-risk disease, 11% for intermediate risk, 43% for high-risk, and 37% for metastatic disease.

Early BCR after RP for PCa occurs in 11–23% of patients after 5 years;[15–17] however, in the present series, BCR occurred in 62.5% (5 of 8 patients) 10.55 ± 20 months after RP. Kimura et el reported BCR after RP in 42.3% of patients ($n = 44$ of 104) with IDC-P after a median follow-up of 6.9 years. Similarly, Miyai et al[18] reported BCR in 36% of patients ($n = 55$ of 151) with IDC-P after RP after a median follow-up of 2 years. BCR after radiotherapy occurred in one of 11 patients according to the Phoenix consensus for BCR, defined as a PSA increase of ≥2 ng/mL above the post radiotherapy treatment nadir; however, four additional patients treated with radiotherapy are under close surveillance for upwardly trending PSA levels and if included, it is likely that the rate of BCR in the radiotherapy cohort will reach 45% in the near future.[9] Van der Kwast et al[19] described BCR in 23% of patients (27 of 118) after radiotherapy for IDC-P after a median follow-up of 6.5 years. The increased risked for BCR in patients with IDC-P emphasizes the importance of discussing the potential for multimodal treatment in this patient cohort at diagnosis.

According to the Swedish family cancer database, PCa is associated with the highest familial cancer rate (20%), followed by breast (13.6%) and colorectal (12.8%).[20] The presence of a positive family history and/or ethnic predisposition (e.g., Afro-Caribbean) are risk factors for PCa.[12] FDRs of PCa patients have a two-fold increased risk for developing the disease compared to the general population.[21] The authors of this study noted a positive family history in eight of the patients (27%). According to the Advanced Prostate Cancer Consensus Conference 2017 guidelines[22] and the Philadelphia Prostate Cancer Consensus conference guidelines,[23] these patients with a family history of PCa should be referred for genetic counseling. These guidelines indicate referrals to genetic professionals in males with a diagnosis of PCa and a family history suggestive of PCa (≥2 PCas on the same side of the family or FDR who has died as a result of PCa <60 years of age or FDR diagnosed with PCa ≤55 years of age or a personal history of PCa diagnosed ≤55 years of age or an FDR with PCa at any age). Furthermore, it has been reported that PCa with DNA repair gene mutation positivity is more likely to be IDC-P and this is most apparent for tumors with mutated BRCA2.[24] In addition, BRCA2 genetic mutations induce a more aggressive PCa[25] and Risbridger[6] also demonstrated that IDC-P is common in patients with familial PCa, BRCA2 mutation carriers have a higher incidence of IDC-P than sporadic PCa and are more likely to have poorer survival outcomes. Taylor et al[26] advised that patients with BRCA2 mutations and IDC-P should be treated aggressively (even with favorable risk disease) because of their genetic instability. Equally important, Antonrakis et al[27] recently suggested that histologic features such as grade group 5 or intraductal carcinoma should prompt evaluation for mismatch repair deficiency (which has a strong association with Lynch syndrome).

Limitations to this study are the retrospective nature and that there may also be under-reporting of IDC-P as indicated by the slightly lower incidence compared to other published data.[28] There may also be a selection bias as this study's cohort consisted of mainly white Caucasian males from a single country. In addition, there is no formal genetic counseling or screening pathway for patients with IDC-P in Ireland and the familial link described herein must be taken on the merit of the phone interviews with patients with IDC-P.

5. Conclusion

The authors demonstrate that IDC-P is associated with more aggressive clinicopathologic features and an increased risk of BCR after treatment. In Ireland, clinical guidelines and a genetic screening pathway are required to provide early detection and appropriate multimodal management of PCa patients diagnosed with IDC-P.

Authors' contribution

U.M. Haroon—protocol and project development, data collection and analysis, as well as manuscript writing and editing; S. O'Grady-Coyne—data collection and analysis; N.F. Davis—manuscript writing and editing; C. Gullman—data collection; J.C. Forde, G.P. Smyth, and I.A. Cheema—project development; R.E. Power—project development and manuscript editing; and L. McLornan—protocol development and manuscript editing.

Research involving human participants and/or animals

This study was approved by the local institutional review board at Beaumont Hospital, Dublin. Informed consent was obtained from all individual participants included in the study.

Conflicts of interest

All authors have no conflict of interest to declare.

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