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Original Article

Ductal Carcinoma of the Prostate: An Uncommon Entity With Atypical Behaviour

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Abstract

Aims: Ductal adenocarcinoma is a rare variant of prostate cancer, and as such clinical outcomes and best management are not well defined. This series demonstrates the atypical presentation and unusual clinical behaviour of ductal adenocarcinoma and proposes management guidelines to assist clinicians.
Materials and methods: A retrospective review of pure (nine patients) and mixed (18 patients) ductal adenocarcinoma of the prostate referred to the Departments of Radiation Oncology of the Sydney Cancer Centre, Royal Prince Alfred Hospital and Northern Sydney Cancer Centre, Royal North Shore Hospital, between 2000 and 2015.
Results: Twenty-seven patients were treated with definitive radiotherapy, nine patients (33%) with pure ductal and 18 (67%) with mixed ductal-acinar adenocarcinoma. The median follow-up was 38 months. Four patients (15%) failed locally, all of whom received less than 80 Gy, or no brachytherapy boost. Five patients (19%) failed distantly, four with biopsy-proven lung metastases. All distant failures occurred with a prostate-specific antigen (PSA) < 3 ng/ml.
Conclusion: This series shows the atypical clinical presentation of this entity, as well as its propensity to metastasise to unusual sites. Relapse may occur at low absolute PSA values and is often asymptomatic. Ductal cancer should not simply be regarded as a high Gleason grade cancer. We propose management guidelines, including regular computed tomography examinations (rather than relying solely on PSA levels) as part of the follow-up for patients with any component of ductal adenocarcinoma.

Key words: Clinical recurrence; ductal carcinoma; follow-up; prostate; radiotherapy

Introduction

Ductal adenocarcinoma is a rare variant of prostatic adenocarcinoma. Pure ductal adenocarcinoma (also previously termed endometrioid, endometrial papillary or papillary ductal adenocarcinoma) has a reported incidence in biopsy and prostatectomy specimens of 0.4–0.8%, whereas mixed ductal-acinar adenocarcinoma has an incidence of up to 5%.

Ductal adenocarcinoma is defined by tall columnar cells arranged in a cribriform, papillary, solid and PIN-like pattern. Under the microscope, pure ductal adenocarcinoma is assigned Gleason pattern 4, and is typically Gleason grade $4 + 4 = 8$ (or $4 + 5/5 + 4 = 9$ if comedonecrosis is present), hence International Society of Urological Pathology (ISUP) grade group 4 or 5. The malignancy may have a patchy basal cell layer, reflecting an intraductal component, and immunohistochemistry for basal cells and alpha-methylacyl CoA racemase (AMACR) may be used to support the diagnosis (Figure 1). Immunohistochemistry for

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prostate-specific antigen (PSA) and prostatic acid phosphatase are typically positive, and the Ki67 proliferative index is high [1].

Classically, ductal adenocarcinoma arises in large primary peri-urethral prostatic ducts. Patients may therefore present with haematuria and/or urinary obstruction, retention or hesitancy [2–4]. In population data, ductal adenocarcinoma has been shown to present with lower mean serum PSA compared with acinar adenocarcinoma, with more than two-fold increased odds of a pretreatment PSA <4 ng/ml [5]. PSA does not accurately predict the clinical stage [6].

At cystoscopy, ductal adenocarcinoma often appears as an exophytic villous/polypoid growth protruding into the urethra at or near the verumontanum [3]. The prostatic urethra may appear narrowed or nodular [1].

Most studies report that ductal adenocarcinoma is more aggressive than its acinar counterpart. The disease has been associated with a higher likelihood of extraprostatic extension, positive surgical margins and shortened time to recurrence after radical prostatectomy [4,7–9]. Ductal adenocarcinoma is also more likely to metastasise, often to unusual sites compared with acinar adenocarcinoma, including the lung, brain and testis [1,8,10]. Ductal adenocarcinoma has a 10-year survival that is inferior to that seen with the typical acinar adenocarcinoma of the prostate [6,8,9].

There are very few reports regarding the outcome of ductal adenocarcinoma managed with radiotherapy in the medical literature. Here we present our outcomes for patients with ductal adenocarcinoma managed with definitive radiotherapy.

Materials and Methods

This retrospective study included all pure and mixed prostatic ductal adenocarcinomas referred to the Departments of Radiation Oncology at the Northern Sydney Cancer Centre and the Sydney Cancer Centre between January 2000 and December 2015. Patients were identified from institutional databases and medical records. Included patients were required to have evidence of ductal adenocarcinoma on biopsy of the prostate or prostatic urethra. All cases included in this report were reviewed by one specialist genitourinary pathologist (JGK). Patients with metastatic disease at presentation were excluded from the analysis ($n = 2$).

Patient demographics were collected from the medical records. Clinical information regarding the presenting symptoms, baseline urological function, PSA, staging investigations and treatments were recorded from hospital databases. Clinical staging was reported as per the AJCC Cancer Staging Manual 7th Edition [11]. The 2014 ISUP grade was used to group patients in addition to Gleason score [12]. Biochemical failure was defined as 2 ng/ml rise in PSA over the PSA nadir [13]. Time to failure, metastatic disease and death were recorded from the date of completion of radiotherapy. Final follow-up data were obtained on 1 October 2017.

Results

Twenty-seven patients were treated with definitive radiotherapy between 2000 and 2015; nine patients (33.3%) with pure ductal adenocarcinoma and 18 (66.7%) with mixed ductal-acinar adenocarcinoma. Two patients were reclassified from pure ductal adenocarcinoma to mixed following pathology review.

Baseline characteristics are summarised in Table 1. The median age at diagnosis was 75 years (range 56–82 years). All patients had good performance status (ECOG 0–1). The median initial serum PSA level was 9.6 ng/ml (range 0.18–25). The Gleason scores ranged from $3 + 4 = 7$ to $5 + 5 = 10$; ISUP grade group ranged from 2 to 5. Baseline urinary function was variable, with International Prostate Symptom Scores (I-PSS) ranging from mild to severe. Nine patients (33%) required a transurethral resection of the prostate (TURP) before radiotherapy. All patients were staged at diagnosis with computed tomography of the chest, abdomen and pelvis and a bone scan.

Most patients were treated with external beam radiotherapy with doses ranging from 70 to 84 Gy in conventional 2 Gy per daily fraction. Two patients underwent high dose rate (HDR) brachytherapy boost (17 or 19 Gy in two

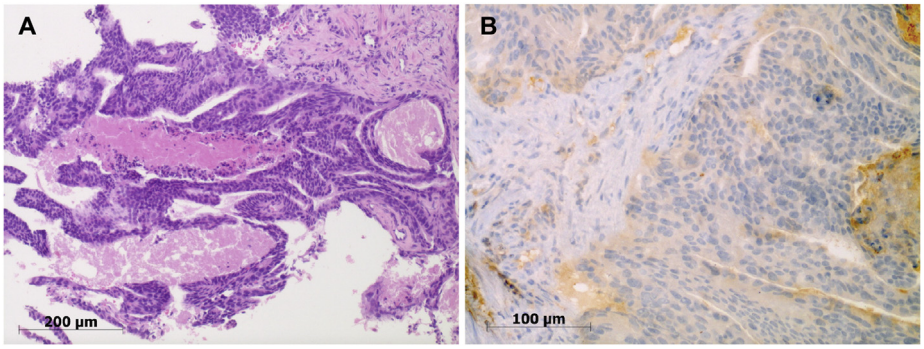

Fig 1. Prostate biopsy showing ductal adenocarcinoma with Gleason score $4 + 5 = 9$ (secondary pattern is 5 due to the presence of focal necrosis) and International Society of Urological Pathology grade group 5 (A) (original magnification 100×). 34betaE 12 immunohistochemistry staining shows lack of basal cells (B) (original magnification 200×).

fractions) combined with 46 Gy in 23 fractions and one had hypofractionated treatment (60 Gy in 20 fractions). Treatment details are summarised in Table 2. Lymph nodes were treated in 15 patients to a dose of 46–60 Gy in 23–40 fractions. Androgen deprivation therapy (ADT) was used in 21 patients for a median duration of 6 months (range 6–60 months). The patient who received 60 months of ADT continued at the discretion of his urologist. The three patients with lymph node metastases received prostate (78–80 Gy) and pelvic radiotherapy (56–60 Gy) combined with 18 months of ADT. One of these patients ceased ADT after 6 months due to toxicity (hot flushes).

The median follow-up was 38 months (range 4–120 months). The single patient who was followed-up for <12 months died at 7 months post-diagnosis due to a haemorrhagic cerebrovascular accident. Three more patients died from unrelated causes (metastatic Merkel cell carcinoma, metastatic colorectal cancer and infection superimposed on myelodysplastic syndrome).

Patterns of recurrence are summarised in Table 3. There were nine failures (33%), four local and five distant, with no biochemical-only recurrence. The median time to failure was 57 months (range 19–83 months). Eight of nine clinical failures (88%) were diagnosed with a PSA < 3 ng/ml. The ninth had a PSA of 4.9 ng/ml.

All local failures occurred in those patients with pure ductal adenocarcinoma, three of whom did not meet the Phoenix definition of failure. Two local recurrences occurred in the prostate and two presented as urethral masses (one at the penile bulb). There were no pelvic lymph node failures. Three of the failures were diagnosed following local symptoms (haematospermia, urinary hesitancy and incontinence) and one on F-18 FDG positron emission tomography (PET) carried out as a component of colorectal cancer staging. The median time to local failure was 74 months (range 51–96 months). All local failures either received doses <80 Gy or did not receive a HDR brachytherapy boost during their initial radiotherapy. Three of these recurrences were managed surgically, whereas one was salvaged with seed brachytherapy. All four men with local recurrence were alive at last follow-up.

Five patients (18.5%) developed metastatic disease, all of whom had mixed ductal-acinar pathology. Four distant failures (80%) included computed tomography-detected (Figure 2) and biopsy-proven lung metastases (Figure 3). Three of these patients had diagnostic computed tomography to investigate respiratory symptoms and one had restaging imaging carried out for a rising PSA (although he had not yet met the criteria for biochemical recurrence). One patient developed skeletal metastases, detected on investigation of back pain. The median time to diagnosis of metastatic disease was 56 months (range 19–57 months) and all five occurred with a PSA level < 3 ng/ml. Two of these patients initially received dose-escalated radiotherapy, whereas three received doses <80 Gy. Four had ADT (for a median duration of 13.5 months), whereas one declined. ADT was started at the time of diagnosis of metastatic disease in all patients. One patient was also given taxotere chemotherapy; another received palliative radiotherapy to the chest to control haemoptysis. One patient subsequently died of ductal adenocarcinoma 3 months after the diagnosis of lung metastases. Two died from unrelated causes. Two were alive at the last follow-up, at 4 and 9 months post-diagnosis of metastatic disease.

Six patients did not receive ADT (22%). One had pre-existing hypogonadism, with a pretreatment testosterone of 2 and remains disease free at 18 months post-treatment. One patient with low volume pure ductal adenocarcinoma was not offered ADT and is disease free at 24 months. Of the remaining mixed ductal-acinar patients, three were recommended for ADT but declined. One patient developed metastatic disease at 56 months, one died of other causes and the third was disease free at 43 months. One patient was not recommended for ADT and died of other causes at 7 months post-treatment.

Discussion

To our knowledge, this is the largest radiotherapy series reporting on ductal adenocarcinoma of the prostate. Our cohort had a higher rate of pure ductal adenocarcinoma than that usually quoted in the literature (33% versus <10%). This may be due to biopsy sampling error, especially as four of the pure ductal adenocarcinoma cohort were diagnosed from TURP chips alone. Due to the rarity of this subtype, the optimal management paradigm is unknown. Several surgical case series have reported high rates of extraprostatic extension (up to 93%) and positive surgical margins (up to 47%) [4,7,9]. As such, patients known to have any amount of ductal adenocarcinoma should either be counselled that there is a high chance that radical prostatectomy will be followed by adjuvant or salvage radiation treatment; that the urologist may plan to dissect more widely; or that definitive radiotherapy treatment is a suitable management option.

Definitive radiotherapy for ductal adenocarcinoma has only previously been described in small case series [14–20]. Eade *et al.* [14] reported an account of six patients managed with radiotherapy (71.8–78 Gy) between 1980 and 2006, five of whom received adjuvant ADT. At more than 3 years of follow-up three patients remained free of biochemical recurrence, whereas two had died of metastatic disease. Four retrospective series evaluated outcomes of ductal adenocarcinoma managed with radiotherapy or radical prostatectomy, with 26, 19, 14 and nine patients in the respective raditherapy groups [15–18]. Three of these series showed better outcomes with radiotherapy, compared with surgery, albeit with small cohorts [16–18]. The fourth found that local control was superior with surgical management, although this series grouped all non-surgical management when analysing outcomes (including watchful waiting and ADT alone) [15]. Forty-two per cent of surgical patients also received radiotherapy as a component of their management, which may have contributed to the lower incidence of locoregional recurrence. Radiotherapy data were missing in 38% of patients. Two papers reported single cases of ductal adenocarcinoma managed with radiotherapy, with

Table 1
Patient demographic and clinical characteristics

Characteristic	Pure ductal adenocarcinoma	Mixed ductal acinar adenocarcinoma
Number of patients (%)	9 (33.33%)	18 (66.67%)
Age, median (range), years	72 (57–82)	75.5 (64–81)
Pretreatment PSA (ng/ml)		
<10	4	10
10–20	3	7
>20	2	1
Presenting symptoms (*n*)		
Asymptomatic	2	7
Lower urinary tract symptoms	1	5
Haematuria	2	4
Lower urinary tract symptoms + haematuria	4	2
T stage (*n*)		
T1	1	4
T2	5	8
T3	2	6
T4	1	0
Nodal stage (*n*)		
N0	8	16
N1	1	2
Gleason score (*n*)		
7	0	4
8	6*	4
9	0	8
10	0	2
Unknown	3	0
ISUP grade (*n*)		
2	0	2
3	0	2
4	6	4
5	0	10
Unknown	3	0

PSA, prostate-specific antigen; ISUP, International Society of Urological Pathology; PIN, prostatic intraepithelial neoplasia.
* Two of these cases were classified as Gleason 4 + 3 = 7 at diagnosis. On pathology review they were upgraded to Gleason 4 + 4 = 8, ISUP 4. In both, focal PIN-like variant was present as well as the more common cribriform/papillary patterns.

Table 2
Treatment details

Characteristic	Value
Radiotherapy technique (*n*)	
Conventional EBRT (2 Gy/fraction)	24
Hypofractionated EBRT (3 Gy/fraction)	1
EBRT + HDR brachytherapy boost	2
Pelvic lymph node radiotherapy (*n*)	
Yes	15
No	12
Conventional EBRT dose (Gy)	
Prostate, median (range)	80 (70–84)
Lymph nodes, median (range)	60 (46–60)
ADT (*n*)	
Yes	21
No	6
ADT duration, median (range), months	6 (6–60)

EBRT, external beam radiotherapy; HDR, high dose rate; ADT, androgen deprivation treatment.

both patients free from biochemical recurrence at 18 months [19,20]. Long-term disease control seems to be achievable, especially when combined with ADT [14,17,18].

Although it is difficult to make definitive management statements based on the small numbers of ductal adenocarcinoma managed with radiotherapy, dose escalation to the prostate and seminal vesicles seems to improve local control. Given the propensity of this disease for

Table 3
Outcome details

Characteristic	Value
Follow-up duration, median (range) months	38 (4–120)
Failure (*n*)	9
Location of disease progression	
Local	4
Distant	5
Both	0

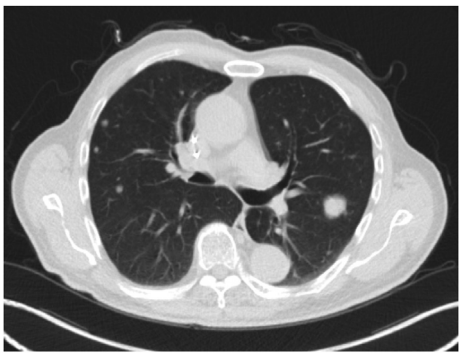

Fig 2. Axial computed tomography image of chest showing bilateral well-circumscribed lung nodules. Biopsy consistent with metastatic ductal adenocarcinoma.

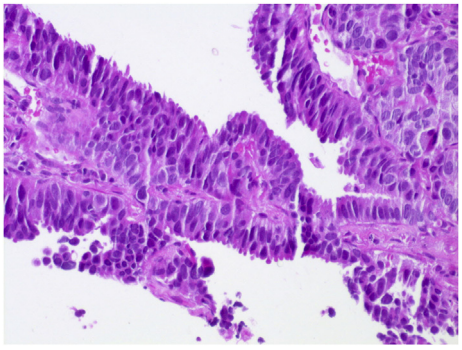

Fig 3. Lung lesion biopsy showing metastatic ductal adenocarcinoma from same case as Figure 1 (original magnification 200×).

extraprostatic extension, radiation oncologists should consider more generous margins in their expansion for microscopic disease than they might for pure acinar cancer. There are mixed data regarding the rate of pelvic lymph node metastases in ductal adenocarcinoma. Retrospective surgical case series report lymph node involvement of 8–27% [2,7]. Although data from the USA SEER registry suggest no increase in lymph node metastases compared with acinar adenocarcinoma [8], a more recent SEER analysis in Asian and Pacific Islander men suggests higher rates of lymph node involvement in ductal adenocarcinoma [21]. As ductal adenocarcinoma is associated with risk factors for pelvic lymph node involvement (ISUP 4 or 5, higher T stage on prostatectomy samples) we recommend elective treatment to the pelvic lymph nodes and consideration of androgen ablation treatment.

In our series, all distant recurrences occurred despite a PSA <3 ng/ml. Four of five patients developed lung metastases, which are uncommon in pure acinar adenocarcinoma. Three of these patients had mild respiratory symptoms (cough, exertional dyspnea) at the time of diagnosis of their pulmonary metastases, one was asymptomatic. Diagnosis was delayed in two patients as their symptoms were initially attributed to infection. Given this unusual presentation, and the low absolute PSA levels, an argument could be made for regular imaging at follow-up using computed tomography of the chest, abdomen and pelvis.

Optimal systemic therapy for metastatic ductal adenocarcinoma is not known. Historically, ductal adenocarcinoma was thought to respond poorly to androgen ablation, but it is now considered to be equivalent to acinar adenocarcinoma [6]. There are few published data on the management of castration-resistant ductal adenocarcinoma. Case reports suggest a mixed clinical response to docetaxel [19,22,23] and abiraterone acetate [23]. In the absence of data, metastatic ductal adenocarcinoma should be managed as per acinar adenocarcinoma.

Ga-68 PSMA PET/computed tomography is being increasingly used to detect prostate cancer, even at low PSA values [24]. However, a single study has shown that ductal adenocarcinoma has variable Ga-68 PSMA avidity, leading to false-negative results [25]. In this scenario, lesions showed increased metabolic activity with F-18 FDG PET. One of our patients had his local recurrence diagnosed incidentally on an F-18 FDG PET. None had routine nuclear imaging as a component of their prostate cancer monitoring. Further studies are required to evaluate the role of PET/computed tomography in the follow-up of this disease.

Based on a review of the literature and our experience (recognising the inherent limitations of a retrospective review of an uncommon clinical entity), we propose the following principles for the management of ductal adenocarcinoma prostate.

Diagnosis

- Staging should include computed tomography chest, abdomen and pelvis due to the high rates of visceral metastatic disease.
- At present there is insufficient evidence to recommend Ga-68 PSMA PET/computed tomography or F-18 FDG PET as staging tools [25].

Management

- Patients being considered for radical prostatectomy should be counselled that there is a higher risk of extraprostatic extension, seminal vesicle involvement and lymph node disease than indicated by conventional nomograms [4,7,9].
- Radiotherapy is a suitable definitive treatment option in the management of ductal adenocarcinoma prostate [14,16–18].
- Doses >80 Gy (in conventional 2 Gy per fraction, delivered daily) or a HDR brachytherapy boost may be important in achieving local control.
- The membranous urethra should be included in the radiation field to the penile bulb, due to the risk of urethral recurrence [18,26,27].
- The seminal vesicles and pelvic lymph nodes should be considered for inclusion in the radiation field.
- TURP should be offered before radiotherapy if there is a urethral mass. Radiotherapy should be delayed for at least 4–8 weeks to allow for the TURP defect to heal [28].

Follow-Up

- PSA is not a reliable tool for assessing failure and the Phoenix definition should not apply to ductal adenocarcinoma, although there is currently no alternative surveillance strategy [5,6].
- In patients who are candidates for systemic salvage therapies, consider using computed tomography chest, abdomen and pelvis as a component of follow-up due to the high rates of visceral metastatic disease [1,8,10].

Conclusion

This series confirms the atypical clinical presentation of ductal adenocarcinoma of the prostate, as well as its aggressive nature. Local failure or metastases occur at low absolute PSA values, without meeting the criteria for biochemical recurrence. Failure may be asymptomatic, further delaying diagnosis. We recommend ductal adenocarcinoma be managed as a distinct subtype of prostate cancer as opposed to being regarded as a high Gleason score tumour. Following definitive radiotherapy, we recommend regular computed tomography examinations as part of scheduled follow-up.

Conflict of interest

None declared.

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