Published in final edited form as:

Cancer. 2007 May 15; 109(10): 2011–2015.

Role of Radiotherapy in Ductal (Endometrioid) Carcinoma of the Prostate

Thomas N. Eade, MBChB, FRANZCR¹, Tahseen Al-Saleem, MD², Eric M. Horwitz, MD¹, Mark K. Buyyounouski, MD, MS¹, David Y.T. Chen, MD³, and Alan Pollack, MD, PhD¹

1 Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania

2 Department of Pathology, Fox Chase Cancer Center, Philadelphia, Pennsylvania

3 Department of Urologic Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania

Abstract

BACKGROUND—Ductal carcinoma of the prostate is a rare variant of prostate cancer that presents most commonly with obstructive urinary symptoms or hematuria. The case series of 6 patients is the first to report the outcome of ductal carcinoma treated with external beam radiotherapy.

METHODS—A retrospective review was performed of patients treated between 1980 and 2006 at Fox Chase Cancer Center, Philadelphia, Penn. Six patients were identified with ductal carcinoma.

RESULTS—Five of the 6 patients were treated definitively and the sixth patient was treated at recurrence 3 years after a radical prostatectomy. Patient ages ranged from 66–80 years and the initial prostate-specific antigen (iPSA) ranged from 1.69–100.3 ng/mL. Three patients had a mixed acinar and ductal carcinoma, 2 with a Gleason score (GS) of 8 and 1 with a GS of 7. Of the patients treated definitively, 4 had clinical stage T2A–T2C and 1 had clinical stage T1B. Definitive radiotherapy was delivered to the prostate with doses between 71.8 Gy and 78 Gy. Pelvic lymph nodes were treated in all patients. One patient was treated post-radical prostatectomy to the prostate bed to a dose of 60 Gy. Adjuvant androgen deprivation was given in 5 of the patients. Two of the patients died from metastatic disease at 1.4 and 7.1 years after treatment. The remaining 4 patients remain alive between 3.2 and 4.8 years from treatment, with 3 patients biochemically without evidence of disease. No patients have developed a local recurrence.

CONCLUSIONS—Ductal carcinoma of the prostate may be treated effectively with external beam radiotherapy. Aggressive management is indicated, even with low-volume metastatic disease.

Keywords

ductal carcinoma; prostate cancer; radiotherapy

Ductal carcinoma of the prostate was originally identified by Melicow and Pachter in 1967.¹ Thought initially to be a neoplastic proliferation of remnant paramesonephric tissue, it was given the name ‘Endometrioid’ carcinoma. More extensive pathologic analysis including ultrastructural studies have determined that these tumors, however, originate from the prostate and are now more correctly termed ductal carcinoma, as a variant of the common acinar adenocarcinoma. Although these tumors are well recognized in the pathologic literature and are generally thought to behave in an aggressive course, there are no reports on outcome after

Address for reprints: Alan Pollack, MD, PhD, Department of Radiation Oncology, Fox Chase Cancer Center, 333 Cottman Ave., Philadelphia, PA 19111; Fax: (215) 728-2868; E-mail: Alan.Pollack@fccc.edu

The contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Supported in part by grants CA-006927 and CA101984-01 from the National Cancer Institute, and a grant from Varian Medical Systems.

radiotherapy or treatment recommendations. We report on 6 patients who were treated at our institution with a diagnosis of ductal carcinoma of the prostate.

MATERIALS AND METHODS

Investigational research board approval was obtained before beginning the study. The Fox Chase Cancer Center prostate cancer database was searched to identify all patients who were seen and treated for prostate cancer between 1980 and 2006. Included patients were required to have evidence of either pure or mixed ductal carcinoma on biopsy of the prostate or prostatic urethra. Six patients were identified from a total of 4521 (0.13%) patients. The pathologic material was reviewed at our institution confirming the diagnosis. Clinical information regarding the presenting symptoms, investigations, and treatments were recorded from the patient charts, including correspondence from treating physicians. Clinical staging was reported as per the AJCC 2002 recommendations.² Time to biochemical failure, metastatic disease, and death were recorded from the date of the completion of radiation therapy. Prostate-specific antigen (PSA) doubling times were calculated pre- and post-radiotherapy where data were available. Target volumes, radiotherapy dose, and the timing and duration of androgen deprivation were also recorded.

RESULTS

The details of each of the 6 cases are provided below. Patient characteristics and treatment details are summarized in Table 1. Patient outcomes are summarized in Table 2.

Patient 1

A 66-year-old Caucasian man presented with obstructive urinary symptoms of increased urgency and nocturia. Digital rectal examination (DRE) revealed a hard nodular prostate bilaterally without extracapsular extension (T2C). His initial PSA (iPSA) was 100.3 ng/mL. A transrectal ultrasound-guided (TRUS) biopsy revealed a Gleason Score 3 + 4 acinar carcinoma in 3 of 6 cores with an associated ductal carcinoma involving 2 of the same cores. No cystoscopy was performed. Initial bone scan and computed tomography (CT) were negative for metastatic disease. The patient was treated with external beam radiotherapy (EBRT) to a dose of 71.8 Gy in 39 fractions to the prostate and 45 Gy in 25 fractions to the pelvic lymph nodes. No hormonal therapy was instigated. After radiotherapy the PSA reached a nadir of 3.2 ng/mL at 6 months. The PSA then started to rise and by 2 years after the completion of RT had reached 18.3 ng/mL, with a doubling time of 5.7 months. Luteinizing hormone-releasing hormone (LHRH) therapy was started. The PSA fell to 3.8 ng/mL. The patient became hormone refractory 2 years after commencing the LHRH therapy. The addition of maximum androgen blockade stabilized the PSA for a short period; however, symptomatic bone metastases were diagnosed 12 months after the addition of Casodex and 62 months after completing RT. Palliative RT between 20 Gy and 30 Gy was delivered on 3 occasions to different painful sites, with a good response. The patient died 2 years after his diagnosis of metastatic disease. He was not known to have developed visceral metastases or local recurrence at the time of death.

Patient 2

A 76-year-old Caucasian man presented with nocturia and dysuria. His iPSA was 4.2. A transurethral resection of the prostate (TURP) was performed and the pathology revealed a ductal carcinoma with comedo architecture. Subsequent clinical examination revealed a bulky, hard prostate bilaterally without extracapsular extension (T2C) and TRUS biopsy of the prostate showed a Gleason 4 + 4 acinar prostate cancer in 1 core. Bone scan and CT scans were negative for metastases. The patient was treated with EBRT to a dose of 72 Gy in 36 fractions to the prostate and 46 Gy in 23 fractions to the pelvic lymph nodes. Concurrent and adjuvant

hormonal deprivation was administered with an LHRH agonist. While still receiving LHRH therapy, and with a PSA <0.1 ng/mL, the patient developed bone and liver metastases 1.2 years after completing RT. Biopsy of both the liver and the bony lesions revealed malignant cells similar to the initial TURP specimen and consistent with metastatic ductal carcinoma. The patient died 2 months after his diagnosis of metastatic disease. His PSA remained undetectable and there was no evidence of local disease.

Patient 3

An 80-year-old Caucasian man presented with gross hematuria and was found to have a frond-like white growth in the prostatic urethra on cystoscopy. Subsequent TURP diagnosed a ductal carcinoma. His PSA had risen from 3.3 to 4.2 in the previous 30 months. No biopsy of the prostate was performed. Before commencing RT, DRE revealed a diffusely hard prostate without extracapsular extension consistent with T2C disease. Staging with a whole-body bone scan and a CT scan of the abdomen and pelvis showed no evidence of meta-static disease. The patient was treated with EBRT to a dose of 78 Gy in 39 fractions to the prostate and 46 Gy in 23 fractions to the pelvic lymph nodes. Hormonal therapy with an LHRH agonist was administered concurrently with the RT and recommended for a further 2 years adjuvantly. The patient continued hormonal treatment for 4.5 years after RT at his own request. At last follow-up, 3 months after completing androgen deprivation, testosterone remained suppressed (32 ng/mL) and PSA remained undetectable. The patient remains without clinical evidence of progression at 4.8 years from RT.

Patient 4

A 73-year-old Caucasian man was found to have a nodule on routine DRE at the left base of the prostate (T2A). His iPSA was 1.69. Biopsy guided by TRUS revealed 1 core positive with a mixed ductal and acinar carcinoma (GS 4 + 4) in the left base. The remaining 5 cores were negative for malignancy. No cystoscopy was performed. There was no history of urinary symptoms and his American Urological Association (AUA) symptom score was 2. RT was delivered to the prostate and pelvic lymph nodes to a dose of 78 Gy and 56 Gy, respectively, in 39 fractions with intensity-modulated RT. Hormonal therapy with an LHRH agonist was administered concurrently with RT and for 2 years adjuvantly. His PSA was undetectable while receiving hormonal deprivation. At the last follow-up, 3.7 years after completing RT, testosterone had returned to within normal limits (533 ng/mL) and he was disease-free, with a PSA of 0.5 ng/mL.

Patient 5

A 70-year-old Caucasian man presented with gross hematuria and cystoscopy revealed a papillary lesion on the floor of the prostatic urethra. Pathology from a transurethral resection was initially diagnosed as a high-grade transitional cell carcinoma of the bladder. A repeat transurethral resection was performed and was reported as ductal carcinoma of the prostate. On review of the initial specimen, the initial diagnosis of transitional cell carcinoma was revised. The patient's iPSA was 6.6 ng/mL. A whole-body bone scan showed no evidence of metastatic disease; however, a CT scan showed 3 lesions within the right middle lobe of the lung and a 4-cm lesion in the upper pole of the left kidney. The patient was started on LHRH agonist therapy with a presumed diagnosis of metastatic renal cell carcinoma. His PSA decreased to 0.2 ng/mL on androgen deprivation therapy. Nephrectomy confirmed a renal cell carcinoma, which did not extend beyond the kidney. Wedge resection of the middle lobe lesions found 1 lesion to be a hamartoma; however, the 2 remaining lesions were metastatic ductal carcinoma. Both of these lesions were positive for CK20, CK7, and PSA, and were morphologically similar to the prostatic lesion. RT was subsequently delivered to the prostate and pelvic lymph nodes to a dose of 78 Gy and 56 Gy, respectively, in 39 fractions with

intensity-modulated RT. Androgen deprivation was continued for 2 years adjuvantly. At last follow-up, 3.6 years after completing RT and 4.2 years after resection of his lung metastases, testosterone had returned to normal (631 ng/mL) and he was disease-free, with a PSA of 0.2 ng/mL.

Patient 6

A 66-year-old Caucasian man presented initially with dysuria. His PSA was 2.8 ng/mL. Cystoscopy showed a mass in the prostatic urethra and after TURP a ductal carcinoma was diagnosed. Biopsy of the prostate did not reveal any definitive carcinoma cells, only cells suspicious for malignancy. The patient proceeded to a radical prostatectomy. The final pathology showed a mixed papillary and cribriform ductal carcinoma involving the left side of the prostate with extracapsular extension and perineural invasion. The seminal vesicles were negative (pT3A), the margins were negative, and 0 of 11 lymph nodes were involved. After surgery the PSA was undetectable. After 10 months the PSA increased to 0.12 ng/mL and by 35 months was 5.1 ng/mL, with a doubling time of 3.4 months. The patient developed hematuria and cystoscopy revealed a recurrence at the bladder neck, which was resected. Pathology confirmed ductal carcinoma. After gross resection the PSA remained elevated at 2.6 ng/mL. RT to the prostate bed and bladder neck was delivered to 60 Gy in 30 fractions, and an LHRH agonist was administered for 16 months. The PSA remained undetectable during hormonal treatment. One year after ceasing hormonal therapy the PSA increased to 0.12 ng/mL and 10 months after this the PSA rose to 11.9 ng/mL (at last follow-up). Androgen deprivation was reinitiated. There was no evidence of local recurrence clinically 3.2 years after RT and 6.2 years after his radical prostatectomy.

DISCUSSION

Ductal carcinoma has been reported in approximately 0.2% of all prostate cancers. The common classic presentation is obstructive urinary symptoms or hematuria due to a prostatic urethral mass; however, ductal carcinoma may also arise in the peripheral or secondary periurethral ducts, either alone or in conjunction with acinar adenocarcinoma. This histological type was initially described as arising from the verumontanum. Architecturally, the cells are similar to endometrioid cancer, which gave rise to the hypothesis that the cells of origin were of remnant embryological origin. The term 'Endometrioid' carcinoma was used until ultra-structure studies revealed both light nonciliated cells and dark ciliated cells within 1 acinus.³ These same investigators also found strong staining for acid phosphatase. The cell of origin is now thought to be prostatic.³

Primary and metastatic ductal carcinoma stains for PSA and/or prostatic acid phosphatase in almost 100% of cases.^{4–8} Mixed acinar and ductal carcinomas occur in 48% to 87% of cases^{4,7,9,10} and may be in distinct components or merged. When diagnosed by needle biopsy, over 50% of the patients will have high-volume disease.⁹ PSA is expressed by ductal carcinoma cells, but is not elevated in all patients. The possibility of PSA production in an associated acinar component also makes interpretation of the PSA difficult and, as such, a normal serum PSA before surgery does not allow prediction of the final pathological stage.⁹ PSA cannot be reliably used to risk-stratify patients.

Christensen et al.¹⁰ reported a detailed account of 15 patients treated initially by radical prostatectomy. The mean age was 63 years and 9 of the 15 patients presented with obstructive urinary symptoms. Although before surgery all of the patients appeared to have resectable disease, the final pathology revealed extracapsular extension in 93% and positive margins in 47%. Pelvic lymph nodes were pathologically positive in 27% and seminal vesicle invasion was found in 40% of the patients. The resected tumors were large, with a mean volume of 8.4 cc and involved a mean of 23% of the prostate. Another series from Johns Hopkins reported

outcomes of 58 patients diagnosed by needle biopsy, of which 20 were treated by radical prostatectomy.⁹ Similar to the previous experience, the extent of the tumors was clinically underappreciated and pathologically 65% had T3 disease, including 2 patients with seminal vesicle involvement. In this series >3 positive cores preoperatively were predictive of positive margins.

Although a number of patients with ductal carcinoma have been treated with RT, there have been no previous reports on doses or response rates. The important observation from our series was the long-term disease control achieved in 5 of the 6 patients, with 4 patients still alive and 3 patients disease-free between 3.6 and 4.8 years. Patient 2 was an outlier, who rapidly developed bony and visceral metastases and died 1.4 years from diagnosis with an undetectable PSA. In all of the patients treated with definitive RT pelvic lymph nodes were included in the initial treatment volume. In no patient was a local recurrence detected. The benefit of hormonal deprivation cannot be gauged from our series, but the addition of androgen deprivation was recommended for all the patients after 1992 (Patient 1). Patient 6 was treated 3 years after radical prostatectomy. On review of this case it is likely that metastatic disease was present before salvage therapy, as the PSA remained elevated despite removal of the recurrent urethral mass. Although not a curative treatment, RT in the setting of gross local recurrence appears to be of benefit for local control.

The natural history of ductal carcinoma is conflicting. Initial reports were of an indolent tumor that in some instances was observed for many years without reported clinical progression.^{1, 11} More recent series have questioned this, reporting ductal carcinoma to commonly behave in an aggressive fashion, with a poor outcome.^{4,5,9,10} The exact role of hormonal deprivation is unknown. Initially the hypothesis of endometrial origin led clinicians to not utilize androgen deprivation in fear of stimulating the tumor growth.¹² Case reports of patients responding to antiandrogen therapy were subsequently described.^{5,7} These findings combined with evidence that the ductal carcinoma cells are of prostatic origin has given rise to the routine use of androgen deprivation. An analysis of the hormonal expression of ductal carcinomas from 12 patients showed estrogen receptor reactivity in none of the 12, with positive staining for androgen receptors in 10 of the patients.⁸ The overall response to androgen deprivation is not as predictable as acinar carcinoma and some tumors will show no response.

Ductal carcinoma of the prostate has been reported to metastasize to lymph nodes and bone, similar to acinar carcinoma,^{4,5} although 2 series have highlighted a more unusual pattern of spread including 8 patients with liver metastases⁶ and 7 patients with metastases to the testicle or penis.¹³ Patient 5 in our series displayed a remarkable history, presenting with synchronous renal cell cancer and metastatic ductal carcinoma to the lung. After resection of the 2 lung metastases, RT to the prostate, and hormonal deprivation the patient is currently disease-free 4.2 years after the resection of his lung metastases. Patients with pulmonary metastases from ductal carcinoma have been reported previously. Millar et al.⁷ described a 74-year-old man who developed pulmonary metastases 2 years after a diagnosis of a papillary ductal carcinoma of the verumontanum. There was a response to androgen deprivation and the patient was alive at 11 years from diagnosis. Gong et al.⁶ reported on 23 patients with metastatic ductal carcinoma, which included 3 patients with pulmonary metastases. Two of these patients remained alive 21 months and 3 months after diagnosis, whereas the third patient died 46 months after diagnosis of his metastatic disease.

Recommendations

Ductal carcinoma of the prostate may be present as a urethral mass or within the prostate and at diagnosis both a cystoscopy and a TRUS prostate biopsy should be obtained if possible. If a urethral mass is present, maximum transurethral resection is indicated before RT Staging with whole-body bone scan and CT of the chest, abdomen, and pelvis should be performed in

all patients. On biopsy, if >3 cores are positive there is a high likelihood of extracapsular extension and positive margins. Due to the possible extensive nature of the local disease, postoperative RT may be required after radical prostatectomy. Because the extent of disease is often underappreciated and PSA levels may not be representative, caution should be used in extrapolating risk models used in acinar carcinoma to make recommendations regarding surgery or definitive RT. As ductal carcinomas are often mixed with an acinar component, are usually bulky, histologically are considered high grade, and may respond to androgen deprivation, we recommend aggressive treatment. Our approach is to administer definitive prostate doses in the 80 Gy range, treatment of the pelvic lymph nodes, and 2–3 years of androgen deprivation in all patients irrespective of iPSA or clinical T-stage. Despite the presence of visceral metastatic disease, long-term disease-free intervals are possible and aggressive local treatment should be considered.

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TABLE 1

Patient Characteristics and Treatment Details

Patient	Age, y	Presentation	iPSA (ng/mL)	AJCC Stage	Mode of diagnosis	Location	Path	Dose prostate	Dose LNs	Hormones
1	66	Urgency Nocturia	100.3	T2B	TRUS Bx	Prostate	GS 3 +4 Ductal Ca	71.8 Gy	45 Gy	At recurrence
2	76	Nocturia Dysuria	4.2	T2C	TRUS Bx; TURP	P Urethra	GS 4 +4 Ductal Ca	72 Gy	46 Gy	Adj recurrence
3	80	Hematuria	4.2	T2C	TURP	P Urethra	Pure Ductal Ca	78 Gy	46 Gy	Adj 54 mo
4	73	Abnormal DRE	1.69	T2A	TRUS Bx	Prostate	GS 4 +4 Ductal Ca	78 Gy	56 Gy	Adj 24 mo
5	70	Hematuria	6.6	T1B	Cystoscopy and TUR	P Urethra	Pure Ductal Ca	78 Gy	56 Gy	Adj 24 mo
6	66	Abnormal cystoscopy	2.8	pT3A	Cystoscopy Radical Prostatectomy	P Urethra Prostate (ECE)	Pure Ductal Ca	60 Gy (Prostate Bed)	NA	Adj 24 mo At recurrence

iPSA indicates initial prostate-specific antigen; Bx, biopsy; P Urethra, prostatic urethra; LNs, lymph nodes; Adj, adjuvant; Mo, months; ECE, extracapsular extension; DRE, digital rectal examination; Ca, cancer; NA, not applicable.

TABLE 2

Treatment Outcomes in All Patients

Patient	Follow-up	Recent PSA	Site of metastasis	Time to metastasis	Time to death
1	7.1 y	NA	Bone	5.2 y	7.1 y
2	1.4 y	NA	Bone; liver	1.2 y	1.4 y
3	4.8 y	<0.1	NA	NA	NA
4	3.7 y	0.5	NA	NA	NA
5	3.6 y	0.2	Lung	At presentation	NA
6	3.2 y*	11.86	NA	NA	NA

PSA indicates prostate-specific antigen; y, years; NA, not applicable.

* 6.2 years following radical prostatectomy.