

Metastasectomy for Isolated Bilateral Adrenal Metastases In Hormone-refractory Prostate Cancer

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A 70-year-old man with a 10-year history of radical prostatectomy followed by postsurgery biochemical relapse 7 years later, which was responsive to androgen-deprivation therapy (ADT; 3-month subcutaneous depot of luteinizing hormone–releasing hormone analog) for 3 years, presented with serially rising serum prostate-specific antigen (PSA) levels. No local recurrence or new skeletal metastases were detected on digital rectal examination and a fresh bone scan. Body imaging with contrast-enhanced abdominal-pelvic computed tomography (CT) scan revealed an increase in size of a previously stable right adrenal mass from 1.5 cm to 4 cm. Magnetic resonance imaging of the adrenal mass was consistent with features suggestive of malignancy. After excluding pheochromocytoma by multiple serologic markers, a fine-needle aspiration of the right adrenal mass was performed, which revealed metastatic adenocarcinoma cytology strongly expressing PSA on immunohistochemistry. The patient was therefore deemed to have progressed to a hormone-refractory stage; systemic chemotherapy consisting of docetaxel and estramustine phosphate was initiated. A partial sustained biochemical response to treatment was immediately observed, which continued for the following 28 months, with a decrease in serum PSA from 39 to 12 ng/mL. Serial radiographic imaging performed during this period also revealed stable adrenal mass size. The patient continued to receive chemohormonal therapy every 3–4 weeks with ADT until a biochemical relapse (serum PSA to 113 ng/mL) prompted a new radiologic evaluation. An increase in size of the right adrenal mass from 4 cm to 6 cm in maximum dimension and a new 4 cm left adrenal mass (Figure 1) were detected with a

contrast-enhanced CT scan. No other systemic soft tissue site or skeletal metastases were detected and serologic markers for pheochromocytoma were found normal. Due to multiple factors, including failure of ongoing chemotherapy, isolated adrenal metastases, a well-maintained patient performance status, and patient concern for cumulative chemotherapy toxicity, laparoscopic bilateral adrenalectomy was performed (Figure 1) to resect a 7 × 8 cm right adrenal gland weighing 81 grams and a 4 × 3 cm left adrenal gland weighing 11 grams (Figure 2A). Malignant involvement of right and left adrenal glands with adenocarcinoma surrounded by normal adrenal tissue (Figures 2B and 2C), with strong PSA immunohistochemistry expression on malignant epithelium (Figure 2D) was detected. Six weeks after surgery, a decrease in serum PSA was noted, from 113 ng/mL to 0.01 ng/mL; serum PSA remained immeasurable 18 months later, with no new evidence of metastasis. The patient was started on replacement steroid doses for adrenalectomy and continues to receive ADT for advanced-stage prostate cancer.

Discussion

Isolated adrenal gland metastasis from prostate cancer is typically a late clinical event during progression. Whereas autopsy series indicate a 20% incidence of prostate tumor metastasis to the adrenal gland¹ in patients dying from widespread systemic disease, solitary involvement from prostate cancer has been rarely reported as an initial presentation of progressive disease.^{2,3} In the case presented, progressive disease was detected in bilateral adrenal glands, with the appearance of a new mass in the uninvolved adrenal gland and a simultaneous increase in size of the contralateral adrenal metastasis. Surprisingly, no other systemic soft tissue deposit or skeletal metastases were found. To our knowledge, this is the first report of

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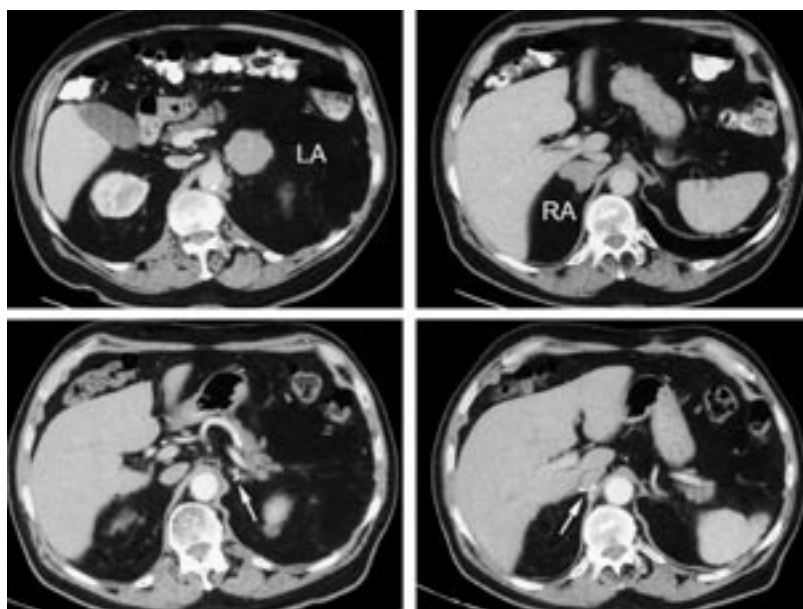


Figure 1. Upper row: Pre-operative left adrenal (LA) and right adrenal gland (RA). Lower row: Arrows point to bilateral post resection surgical clips.

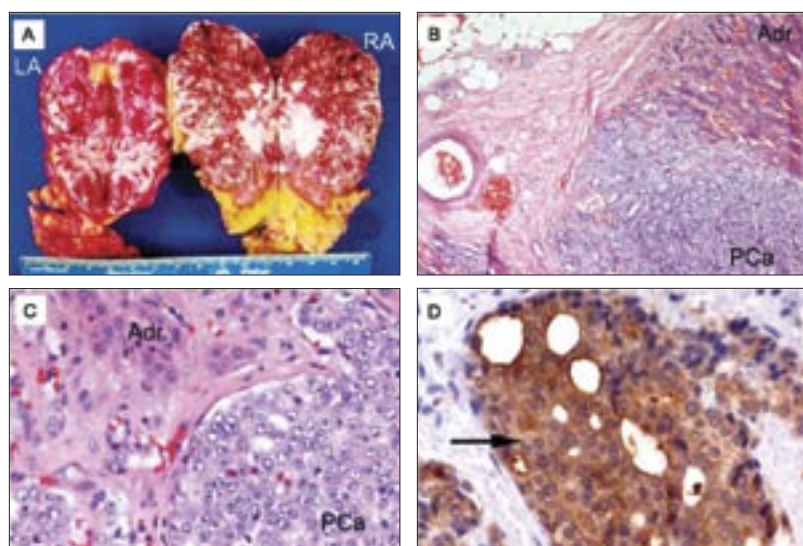


Figure 2. (A) 7 cm × 8 cm right adrenal (RA) gland weighing 81 g and 4 cm × 3 cm left adrenal (LA) gland weighing 11 g. (B-C): 100× and 400× magnification with adenocarcinoma (PCa) cells and normal adrenal (Adr) tissue on H/E immunohistochemistry. (D) Arrow shows strong PSA-positive immunohistochemistry expression on metastatic malignant epithelium (400×).

isolated bilateral adrenal metastasis in hormone-refractory prostate cancer.

Laparoscopic bilateral adrenalectomy was performed after careful consideration of the patient's clinical presentation. These included lack of detectable extra-adrenal disease, patient concern of cumulative chemotherapy toxicity, a prolonged time to progression after initiating chemotherapy, and available expertise for conducting a relatively less invasive procedure compared to open surgery. The rapid and sustained PSA decline at last follow-up (18 months) postoperatively indicates a favorable outcome to the surgical intervention in terms of overall palliation benefit despite a high probability of distant micrometastases and systemic recurrence. Metastasectomy

in advanced prostate cancer, though not a usual management strategy, has been previously reported³ for unilateral adrenal metastasis and may provide palliation in patients carefully selected according to criteria yet to be defined.

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Review

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Kohli and colleagues¹ describe a 70-year-old man who presented with biochemical recurrence of prostate cancer 7 years following a prostatectomy. He had received treatment with ADT for 3 years, at which point androgen-independent prostate cancer (AIPC) was diagnosed by rising PSA. A restaging evaluation noted growth of a previously appreciated adrenal mass from 1.5 to 4 cm, which was confirmed to be metastatic adenocarcinoma consistent with prostate primary. Chemotherapy with docetaxel and estramustine was administered and associated with a decrease in PSA from 39 to 12 ng/mL and stabilization of the adrenal mass. After 28 months, progressive disease was noted by rapid increase in PSA to 113 ng/mL, an increase in size of adrenal mass from 4 to 6 cm, and a new 4-cm contralateral adrenal mass. No other sites of disease were found following a restaging evaluation. A decision was made to treat the patient with bilateral laparoscopic adrenalectomy, which was associated with brisk decline in PSA from 113 to 0.01 ng/mL in 6 weeks and sustained for 18 months of follow-up at the time of this report.

This case highlights several important points relevant to the care of patients with recurrent prostate cancer, especially relating to the long natural history of the disease and the importance of individualized, patient-focused therapy.

The natural history of recurrent prostate cancer presented here is consistent with outcomes in many large case series. A study of 1997 patients with a median follow-up of over 5 years reported a metastasis-free survival rate of 82% after 15 years, a median time from surgery to biochemical recurrence of 8 years, and a median time from biochemical recurrence to prostate-specific mortality of 5 years.² This study, and others, highlight the importance of pathologic variables (Gleason score, clinical and pathologic stage) and postoperative follow-up (time from primary therapy to biochemical recurrence, PSA nadir, and PSA doubling time) as strong predictors of long-term disease-specific mortality.²⁻⁵ In this report, a particularly long latency between surgery and biochemical relapse of

7 years is noted. Though other relevant data to predict cancer-related outcomes are not given, the long latency from surgery to biochemical recurrence is at least one factor predictive of a relatively long disease-specific survival. In summary, the 10 years from surgery to recurrent disease and subsequent 3 years of follow-up with isolated adrenal metastasis exhibited in this patient is generally within a range expected for patients with recurrent prostate cancer, particularly with multiple favorable prognostic variables.

The main feature that distinguishes this patient from the vast majority of patients with prostate cancer is the unusual pattern of metastatic spread, specifically isolated soft tissue disease in the adrenals and the absence of bone lesions. Although adrenal metastasis in prostate cancer may be found in up to 25% of patients at autopsy, they are usually found in the setting of widespread bone and visceral disease.⁶ Confirming the “bone tropism” of prostate cancer, large multisite trials in AIPC report bone metastatic disease in approximately 85–90% of patients, with isolated measurable disease noted in the remaining 10–15%.⁷⁻⁹ If measurable disease is present, it most commonly consists of lymphadenopathy, followed by rarer occurrences of lung or liver metastasis.⁹ Therefore, the finding of isolated adrenal metastasis is exceedingly rare and makes this case exceptional in comparison with most patients with AIPC.

With this unusual manifestation of AIPC, the management of this patient is of particular interest. Clinical progression (as evidenced by PSA and objective progression in imaging studies) after first-line chemotherapy with docetaxel/estramustine was treated with bilateral adrenalectomy in an attempt to remove all measurable disease. Options for systemic therapy following docetaxel-based chemotherapy for AIPC are decidedly limited.¹⁰ As an anticancer treatment, resection of all sites of gross disease may seem appealing. One can imagine that any large, measurable tumor may be resistant to therapy due to decreased chemotherapy penetration and a relatively hypoxic environment. In addition, large tumors may provide a reservoir of cancer cells that can acquire additional molecular changes associated with chemotherapy resistance and increased metastatic potential. Data supporting the role of tumor resection in common epithelial malignancies, such as colon or breast histologies, are relatively limited owing to the difficulty of performing prospective randomized trials. However, uncontrolled studies tend to support the role of tumor resections in select patients when systemic disease is otherwise controlled and tumor recurrence is isolated to one organ.^{11,12} Aside from the isolated report of adrenalectomy described by the authors, further review of the literature reveals only one other case of metastasectomy for pulmonary disease with no specific information for follow-up.^{13,14} Therefore, this report is

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particularly important in describing the potential benefit of metastasectomy for a patient with prostate cancer.

Recent advances in laparoscopic surgery have conferred benefits on the surgical management of adrenal tumors. Metastatic adrenal tumors are often well-contained in the adrenal capsule (as was found on the pathology in this case) and therefore amenable to laparoscopic resection. This report of progression-free survival of 18 months following laparoscopic adrenalectomy compares favorably to a recent collection of case series for laparoscopic adrenalectomy with other primary histologies.¹⁴ With longer follow-up, one could predict that the disease-free survival for this patient may approach among the longest on record.

In summary, this important case report highlights the long natural history of patients with recurrent, even metastatic AIPC. In this very select case, the patient exhibited dramatic disease control with metastasectomy of adrenal disease. Treatment for prostate cancer that recurs following surgery should be informed by studies that predict the variable natural history of these patients and individualized local or systemic therapy should be administered as appropriate.

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