Case Series

Complete response in Patients With Lung-Only Metastatic Prostate Cancer: Outcome Analysis

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Abstract

Lung-only metastatic prostate cancer can be seen in 4.6% of patients and historically patients with visceral metastastic disease are considered high risk. In order to determine survival outcomes in this patient population, we conducted a restrospective review of patients with metastatic hormone sensitive prostate cancer with lung-only metastases. In this single institution review, 10 patients were identified with 8 achieving a complete response and 2 achieving a partial response when treated with androgen deprevation therapy (ADT) with or without metastastetomy. The median progression free survival was 64.4 months with 8 of these patients (80%) with ongoing complete response at time of follow-up. Lung-only metastases may serve as a good prognostic characteristic which will allow the clinician to treat with ADT alone with or without surgery to minimize treatment realted toxicity and still offer the ability to achieve a complete response with prolonged survival.

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Introduction

Regional lymph nodes and bone metastases have been established as the most common sites of metastatic disease for prostate cancer. Atypical sites of metastases are also seen with the most frequent sites occuring in the lungs (46%), liver (25%), and adrenal glands (13%), based on a postmortem analysis of 19,316 patients.[1] Visceral metastases have been included as part of high burden disease criteria and therefore, high-risk for poor prognosis.[2] In postmortem patients with prostate cancer, lung-only metastases is seen in approximately 4.6% of patients and several case series and reports have suggested a more favorable prognosis with durable responses to androgen deprivation therapy.[3-12] We present a single institution cohort outcome analysis of 10 patients with lung-only metastatic hormone sensitive prostate cancer (mHSPC) who were treated with androgen deprivation therapy (ADT) with or without surgery.

Patients and Methods

A retrospective review of patients at Mayo Clinic Florida was performed from 2001 to 2021 and identified 10 patients with prostate cancer who had lung-only metastases without the presence of pathologically enlarged lymph nodes (PCWG3 criteria), bone or other visceral metastases. Lung-only metastatic disease was determined based on conventional imaging and underwent confirmation of prostate orgin via biopsy or pathologic evaluation postsurgery (Figure 1). Patient and disease characteristics were collected. The response to treatment, partial response (PR) or complete response (CR), was documented based on prostate specific antigen (PSA) and conventional imaging via computed tomography (CT) imaging and bone scintigraphy. Duration of response was calculated from the time of first undetectable PSA after metastases directed therapy (systemic treatment or surgery) or time from surgery to last follow up with no evidence of disease, as determined by undetectable PSA (<0.1 ng/mL) and no metastatic disease on conventional imaging. No financial support was provided for the collection or analysis of this study.

Results

The patients in this cohort received primary definitive treatment with either radical prostatectomy, external beam radiotherapy or seed implantation. Of the patients where Gleason score was known (n = 9), 1 patient had Gleason 6 (11%), 3 had Gleason 7 (33%), 2 had Gleason 8 (22%) and 3 had Gleason 9 (33%) disease. Five out of 10 patients went on to develop biochemical recurrent prostate cancer prior to metastatic disease and treated with intermittent ADT and/or salvage radiotherapy. The average PSA at time of metastatic disease was 3.1 with a range from 0.8 to 11.2. Of the 10 patients with lung-only metastatic disease, 3 had a single metastatic lesion, 3 had multiple lesions in 1 lung, and 4 patients had bilateral metastatic lung nodules.

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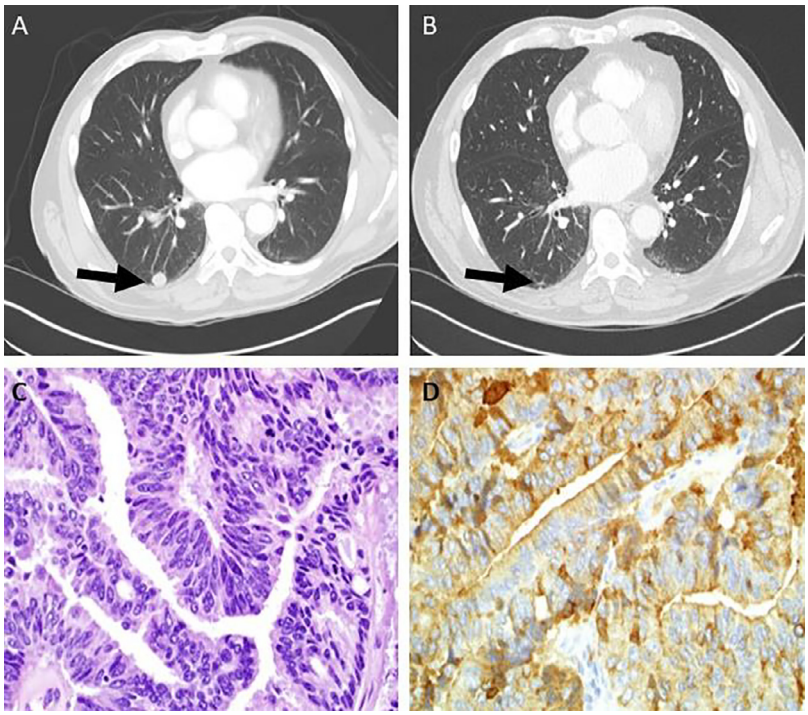
Figure 1 (A-D) Imaging and Pathology. (A) CT imaging revealing metastatic lung lesion from case 1 (pretreatment) and CT imaging showing complete response posttreatment with ADT alone (B). (C) High power view of metastatic lung lesion demonstrating tall and columnar tumor cells with cytologic features for prostate ductal adenocarcinoma. (D) Immunohistochemistry for prostate specific antigen (PSA) showing cytoplasmic staining, confirming prostate primary.



All patients (n = 10) achieved a partial or CR following treatment for lung-only metastatic prostate cancer (Table 1). Two patients (case 9 and 10) achieved a partial response with leuprolide. Case 9 was started on ADT following right lower wedge resection and PSA decreased from 0.8 to 0.3, however, did not achieve undetectable PSA levels. The partial response lasted 34 months before the patient progessed with evidence of new pulmonary nodules. Abiraterone with prednisone was added to ADT and the patient achieved an undetectable PSA and no evidence of disease on imaging consistent with complete response. The complete response has lasted 38 months and is ongoing. Case 10 achieved undetectable PSA after 1 year of ADT with leuprolide and metastatic lung lesions decreased in size, but did not completely resolve consistent with partial response which is ongoing for more than 8 months. Both patient's achieving a partial response had biochemical recurrence prior to the development of metastatic disease.

Eight patients (80%) achieved a complete response with ADT alone (n = 4) or surgery plus ADT (n = 4) with 7 of the 8 patients having ongoing complete response (Figure 2). Three patients (38%) had biochemical recurrence prior to metastatic disease including the patient who progressed after achieving CR (case 8). Case 8 achieved a CR which lasted 4 months before developing metastatic bone disease. Due to patient preference, he has remained on ADT monotherapy and remains alive 48 months after the development of metastatic disease to the lung. Excluding the patient (case 8) who progressed after 4 months, the average duration of ongoing complete response is 80 months or 6.7 years with the longest ongoing duration equaling 175 months or 14.5 years. For all 10 patients achieving a PR or CR, the average time from primary diagnosis of prostate cancer to lung only metastasis was 106 months or 8.8 years. The median progression free survival for all 10 patients with first treatment is 64.4 months, ranging from 4 months to greater 183 months with 8 of these patients having continued response at time of follow up or nonprostate cancer related death.

Discussion

The findings presented in this restrospective study examine the response rate and survival in prostate cancer patients with lung-only metastases treated with androgen deprivation therapy alone. The results demonstrate a complete response rate (80%, n = 8) after first systemic treatment with ADT alone excluding the patient who achieved a CR after the addition of abiraterone to ADT. In addition, these 10 patients with CR or PR achieved a prolonged progressive free survival averaging 64.4 months with ongoing survival. This survival data exceeds outcomes seen in patients with metastatic hormone sensitive prostate cancer who were treated with ADT alone. Patient's with metastatic hormone sensitive prostate cancer have multiple treatment options available which have proven to improve progression free survival and overall survival including: abiraterone, enzalutamide, apalutamide and docetaxel.

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Table 1 Patient and Tumor Characteristics

Case	Response	Duration of Response (mo)	PFS (mo)	Time from Primary Diagnosis to Lung Metetastases (mo)	Primary Prostate Treat-ment	Gleason Score	History of BCR	BCR Treat-ment	PSA at Time of Metastatic Disease	Metastatic Disease Description	Metastatic Systemic Treat-ment	Surgery
1	CR	34[a]	34[a]	54	EBRT	7	No	n/a	2.7	Several metastatic nodules, largest measuring 16 mm	ADT	n/a
2	CR	118[a]	118[a]	131	RP	8	Yes	Intermittent ADT	Unknown	13 mm lung nodule	ADT	Lobectomy
3	CR	87[a]	87[a]	35	RP	7	Yes	Salvage RT	0.82	11 mm and 8 mm right lung nodules	ADT	n/a
4	CR	63[a]	63[a]	51	EBRT	9	No	n/a	0.8	Multiple bilateral lung odules, largest 10 mm	ADT	n/a
5	CR	20[a]	28[b]	75	EBRT	Unknown	No	n/a	2.1	Bilateral pulmonary nodules, largest 19 mm	ADT	n/a
6	CR	69[a]	82[b]	0	Seed Implant and EBRT	9	No	n/a	Unknown	Left lobe nodule 17 mm	None	Left upper lobectomy
7	CR	175[a]	183[b]	126	EBRT	9	No	n/a	3.7	Right lobe nodule 14 mm	ADT	Right middle lobectomy
8	CR	4	4	262	RP	6	Yes	Salvage RT and Intermittent ADT	11.2	Multiple left lower lobe nodules, largets 29 mm	ADT	Left lower lobectomy
9	PR[c]	34	34	218	RP	8	Yes	Intermittent ADT	0.8	Multiple right lower lobe nodules	ADT	Right lower wedge resection
10	PR	8[a]	11[a]	111	RP	7	Yes	Salvage RT	2.6	Bilateral lung nodules, largest 17 mm	ADT	n/a

Abbreviations: ADT, androgen deprivation therapy; BCR, biochemical recurrence; CR, complete response; n/a, not applicable; PFS, progress free survival; PR, partial response; RT, radiotherapy.
[a] Ongoing response at last follow up.
[b] Died of causes not related to prostate cancer.
[c] Achieved CR with addition of abiraterone/prednisone to ADT after first progression and has a CR lasting 38 mo and ongoing.

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Figure 2 Swimmers plot showing duration of response.

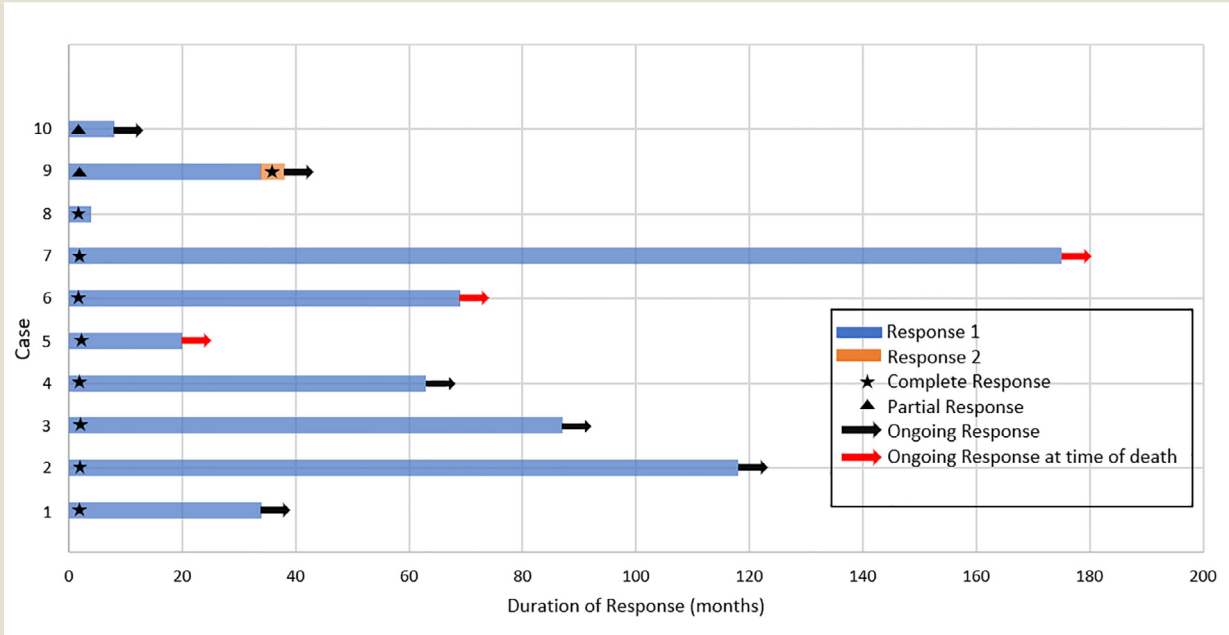

Table 2 Comparison of Treatment Duration Between our Study Presented Here (Kase et al) and Other Studies Treating Patients With Metastatic Hormone Sensitive Prostate Cancer

Study	Treatment Arm	Staging Description	Treatment Duration(mo)
Kase et al	ADT alone ± surgery	Lung-only metastases	64.4
Shenderov et al	ADT alone	Lung-only metastases	66
ARCHES[19]	Enzalutamide + ADT	mHSPC	40.2
ARCHES[19]	ADT alone	mHSPC	13.8
CHAARTED[2]	Docetaxel + ADT	mHSPC	20
CHAARTED[2]	ADT alone	mHSPC	12
LATITUDE[19]	Abiraterone/prednisone + ADT	mHSPC	33
LATITUDE[19]	ADT alone	mHSPC	14.8
TITAN[18]	Apalutamide + ADT	mHSPC	39.3
TITAN[18]	ADT alone	mHSPC	20.2

Duration of treatment defined as, PSA-PFS, rPFS, progression or unacceptable toxicity.
Abbreviations: mHSPC, metastatic hormone sensitive prostate cancer; PSA, prostate specific antigen; PFS, progression free survival.

In the LATITUDE trial, abiraterone was given to patients with 2 high risk features including Gleason score ≥8, ≥3 bone lesions or measurable visceral metastasis. The median overall survival was 53.3 months in the abiraterone/prednisone plus ADT group and 36.5 months in the placebo plus ADT group.[13] In the TITAN trial with apalutamide 63% of patients had high volume disease based on visceral metastasis plus ≥1 bone lesion, or ≥4 bone lesions with at least 1 outside axial skeleton. The 2-year overall survival in the entire cohort was 82.4% in the apalutamide ground versus 73.4% in the ADT group.[14] In the ARCHES trial, where men with de novo or relapsed mHSPC were randomized to enzalutamide plus ADT or ADT alone, the median treatment duration was 40.2 months in the combination group and 13.8 months in the placebo plus ADT group.[15] In this trial, bone plus lymph node metastases patients had a radiologic progression free survival (PFS) of 14 months. Eleven percent of patients had visceral metastases with lung without liver metastases being the most common (75%). The survival data in these trials represent patients with metastatic disease regardless of location, however, not all metastatic disease sites have the same outcomes. In a post hoc analysis of the ARCHES trial, patients with visceral ± bone or lymph node metastases had a less pronounced response to enzalutamide and ADT as the confidence interval crossed 1.0. In a subgroup analysis of patients with lung metastases only, the radiologic progression hazard ratio was 0.79 when comparing enzalutamide plus ADT to ADT alone, however, not signficant.[16] Apalutamide also showed an unclear benefit when

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added to ADT in the setting of visceral metastases.[13,14] Abiraterone showed a survival benefit in the subgroup analysis visceral metastatic setting with a hazards ratio (HR) 0.58 (95% confidence interval [CI] 0.41-0.83) and in the CHAARTED trial docetaxel showed a trend toward survival benefit in the subgroup analysis for visceral metastases with or without bone metastases with HR 0.52 (95% CI 0.25-1.07). While the clinician should consider abiraterone or docetaxel for high disease burden with visceral metastases, lung-only metastases appears to have a better prognosis even with ADT alone.[6-9,17]

Shenderov et al reviewed genomic and clinical characteristics of lung-only metastatic prostate cancer and found patients on first line ADT had a 4-year survival of 72% with 7 of the 18 patients having ongoing response. Only 3 of their patients had complete radiographic response.[17] Lung-only metastatic prostate cancer has been shown to have actionable mutations with 50% having any DNA-repair gene alteration, 25% homologous recombination deficiency, and 25% with loss of function mutatsion in missmatch repair genes.[17] This genomic profile may make these patients more responsive to ADT alone. When compared to FDA approved treatments for mHSPC and the control arms in each of these studies, lung-only metastases treated with ADT alone ± surgery has a better prognosis (Table 2).[18] The progression free survival in our study was 64.4 months with 8 of the 10 patients with on going response is similar to the PSA-PFS of 66 months reported by Shenderov et al. The observational study presented here suggests ADT with or without surgery could be utilized to minimize toxicity and preserve androgen signaling inhibitors if relapse or progression occurs as they may still achieve complete response after ADT as shown in case 9.

Conclusion

Metastatic prostate cancer has been shown to be a heterogenous disease process as seen by the varying survival outcomes based on metastatic disease location. In this retrospective review, we have identified prostate cancer patients with lung-only metastases who obtained an excellent response to ADT with or without surgery with ongoing response. Lung-only metastases may serve as a good prognostic patient characteristic which will allow the clinician to treat with ADT alone to minimize treatment realted toxicity and still offer the ability to achieve a complete response.

Clinical Practice Points

- The management of metastatic prostate cancer should be based on disease burden and disease location which has an impact on prognosis.
- Lung-only metastatic prostate cancer appears to be a good prognostic indicator allowing for ADT with or without surgery to be an effective treatment option to achieve a complete and durable response.

Disclosure

The authors have no conflicts of interests to disclose.

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