

# Curative Lung Metastasectomy Without Concomitant Androgen Deprivation Therapy in Oligometastatic Castration-resistant Prostate Cancer: A Case Report and Review of the Literature

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## Clinical Practice Points

- The very few reports currently available in the literature show that an active approach, with curative intent, to lung metastasis from prostate cancer can be beneficial in terms of biochemical response and disease-free survival.
- Stereotactic body radiotherapy, associated with androgen deprivation therapy (ADT), represents the most experienced treatment option in such patients, whereas ADT alone is still the gold standard of care.
- We present a case of oligometastatic castration-resistant prostate cancer in a patient who was successfully managed by surgical pulmonary metastasectomy followed by ADT interruption.

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## Introduction

Prostate cancer (PC) metastases commonly involve bones and lymph nodes (90%), whereas the presence of metastases in other organs, such as lungs and liver, often correlates with a worse prognosis and a high burden of disease, amounting to the clinical setting of polymetastatic PC.<sup>1,2</sup>

On the other hand, the most common definition of oligometastatic tumor is the presence of 1 to 5 metastases in less than 2 organs.<sup>3,4</sup> In patients with oligometastatic disease by breast, kidney, lung, or colorectal neoplasms, ablative surgery or radiation therapy may be potentially curative, sometimes in association with adjuvant

systemic treatments.<sup>4</sup> Conversely, in patients with oligometastatic PC, ablative treatments are currently not indicated, except for clinical trials.<sup>5-7</sup> In these patients, androgen deprivation therapy (ADT), achieved with surgical bilateral orchiectomy or luteinising hormone-releasing hormone (LHRH) agonist/antagonist, is still the standard treatment, according to international guidelines.<sup>7,8</sup>

However, related adverse events, such as hot flashes, vasomotor instability, osteoporosis, fatigue, cardiovascular morbidity, psychological and cognitive disorders, and metabolic syndrome, may compromise quality of life, particularly if ADT is administered for several years.

Here, we describe a clinical case of a patient with PC, who underwent prostatectomy and subsequent adjuvant radiotherapy and ADT, who later progressed to an oligometastatic castration-resistant disease, characterized by 2 lung metastases, which were radically resected through surgery, followed by ADT (LHRH agonist) withdrawal.

## Case Presentation

In March 2005, a 63-year-old man with severe lower urinary tract symptoms and without comorbidities presented with a prostate-specific antigen (PSA) of 9.1 ng/mL and a prostatic biopsy

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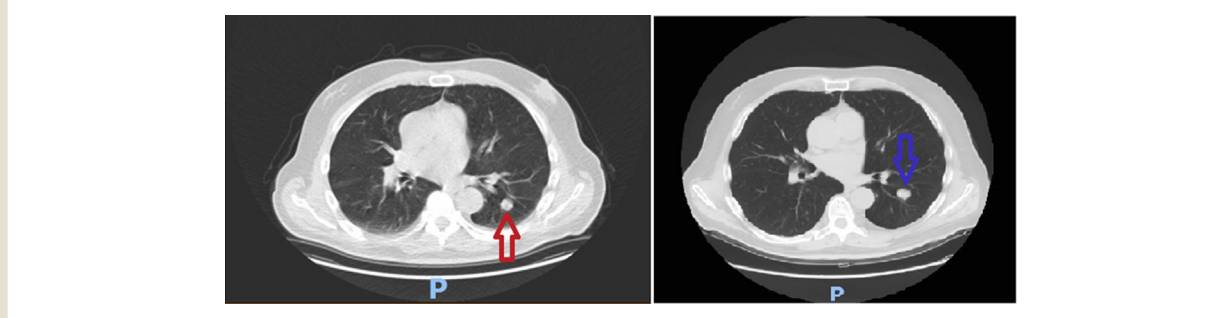
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**Figure 1** Computed Tomography Scan Showing 2 Left Lung Metastasis (Blue and Red Arrows)

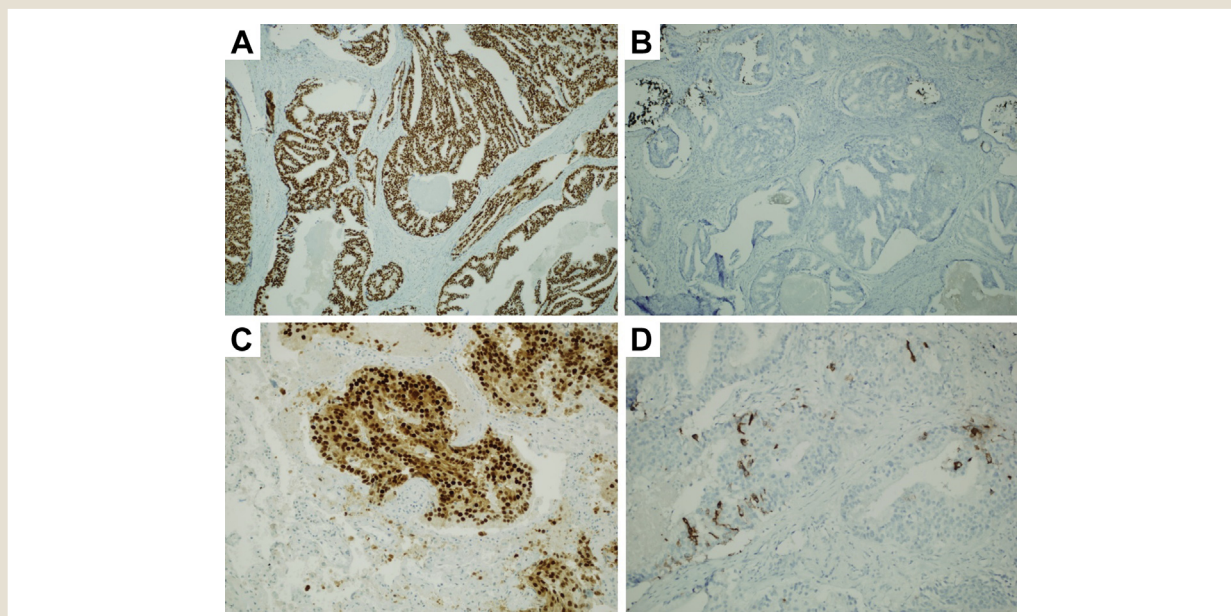
negative for PC, and therefore underwent prostatic adenectomy. Histologic examination revealed a benign prostatic hyperplasia associated with a prostatic adenocarcinoma in more than 5% of tissue resected, with diffuse and intense nuclear positivity for androgen receptors, Gleason Score 8 (5 + 3).

He started bicalutamide (150 mg daily) from March to October 2005, and he completed external beam radiotherapy (74 Gy) on the prostate bed in September 2005. Post-radiotherapy PSA decreased to a nadir of 0.03 ng/mL in 2007, but it rose to 0.35 ng/mL in 2012, 84 months after radiotherapy.

In 2013, owing to cough, he underwent thorax radiography, which showed 2 pulmonary micronodules requiring active surveillance. In the following months, PSA increased to 1.32 ng/mL. A computed

tomography scan performed at the beginning of 2014 pointed out 2 pulmonary lesions (diameters of 15 and 16 mm, respectively), confirmed by a fluorodeoxyglucose-positron emission tomography and corresponding to the micronodules previously highlighted by the radiography (Figure 1). In April 2014, the patient underwent a transthoracic biopsy, which demonstrated metastases from prostatic adenocarcinoma (PSA+, CK7+/-, TTF1-, CDX 2-) and was started on ADT with LHRH agonist. After an initial response, with a PSA lowered to < 0.09 mg/mL, the PSA further increased to 0.25 ng/mL, and a computed tomography scan revealed a volumetric progression of pulmonary metastasis 2 years later.

From January to November 2016, the patient started total androgen blockade, adding bicalutamide 50 mg daily to LHRH

**Figure 2** A, Diffuse and Intense Nuclear Positivity for Androgen Receptor in the Primary Prostatic Adenocarcinoma (100×, Androgen Receptor Immunostaining); B, Complete Negativity for Cromogranin-A in the Primary Prostatic Adenocarcinoma. (100×, Cromogranin-A Immunostaining); C, Diffuse and Intense Nuclear Positivity for Androgen Receptor in the Lung Metastasis. (200×, Androgen Receptor Immunostaining); D, Isolated and Rare Cells Positive for Cromogranin-A in a Small Area of the Lung Metastasis (200×, Cromogranin-A Immunostaining)

**Table 1** Literature Review of Pulmonary Metastasis From PC Managed With Surgical Ablation

Author	TN Stage	Gleason Score	Initial Management	Metastases	ADT	Metastatic Management	Follow-up
Smith <sup>11</sup>	T2N0	4 + 5	RP	Single, 2 cm	No	Surgical resection	PSA undetectable
Wallis <sup>12</sup>	T3aN0	4 + 5	RP + RT	Single, 1 cm	No	Surgical resection	PSA decreased to 0.3 ng/mL at 1 year
Chao <sup>13</sup>	T2aN0	4 + 5	RP	Single, 1.2 cm	No	Wedge resection	Disease-free at 12 years
Pruthi <sup>14</sup>	T2bN0	3 + 3	RP + RT	Single, 2 cm	LHRH agonist	Surgical resection	PSA undetectable at 3 years
Khandani <sup>15</sup>	NA	NA	RT	Single, NA	No	Surgical resection	PSA decreased to 0.2 ng/mL
Hofland <sup>16</sup>	T2cN0	4 + 5	RP + RT	Single, NA	Bilateral orchiectomy	Surgical resection	Further metastases developed/lost at follow-up
Boyer <sup>17</sup>	T2NX	3 + 3	RP	Single, 2.8 cm	Leuprolide	Surgical resection	PSA decreased at 0.07 ng/mL
Bromberg <sup>18</sup>	NA	3 + 3	RP	Three, NA	Bilateral orchiectomy	Wedge resection	Resolution of nodules within 1 year
Maeda <sup>19</sup>	T2bN0	NA	RP	Two, NA	No	Surgical resection	NA
Cusan <sup>20</sup>	NA	NA	RT	Bilateral, NA	LHRH agonist and flutamide	Surgical resection	PSA decreased to 0.5 ng/mL
Behrakis <sup>21</sup>	NA	NA	TURP	Three, NA	GnRH agonists	Open lung biopsy	Resolution of pulmonary metastasis within 8 months
Maebayashi <sup>22</sup>	T4 N0	4 + 5	RT	Single, 3 cm	Goserelin acetate and bicalutamide	Surgical resection + Paclitaxel and Carboplatin + Mediastinal RT	Dead from mPC at 30 months
Rush <sup>23</sup>	T4N0	4 + 4	RP	Single, 4.7 cm	No	Surgical resection	PSA undetectable at 24 months
Pepe <sup>24</sup>	T3aN0	4 + 3	RP	Single, 2 cm	No	Surgical resection	Free from recurrences at 6 months
Goto <sup>25</sup>	NA	4 + 5	RP	Single, NA	Maximum androgen blockade	Wedge resection	Free from recurrences at 10 months
Mortier <sup>26</sup>	T3aN0	3 + 3	RP + RT + Androgen deprivation therapy	Single, 2 cm	ADT (interrupted at 1 year)	Surgical resection	PSA undetectable at 1 year
Boschian <sup>27</sup>	T3aN0	4 + 3	RP + RT	Single, 1 cm	No	Surgical resection	PSA undetectable at 36 months
Gago <sup>28</sup>	T3aNx	NA	RP + RT	Single, NA	LHRH agonist	Surgical resection	No recurrences at 5 months
Reinstatler <sup>29</sup>	T1Nx	4 + 4	TURP	Multiple, max 2-3 mm	Leuprolide + docetaxel	Surgical resection	NA
Ciriaco <sup>30</sup>	T3bN0	4 + 4	RP	Three, NA	ADT	Wedge resection	Clinical recurrence at 6 months
	T2bN0	5 + 2	RP + RT + Chemotherapy	Three, NA	No	Wedge resection	Biochemical response at 85 months
	T2bN0	5 + 3	RP + RT	Single, NA	No	Wedge resection	Biochemical response at 11 months
	T3aN0	4 + 4	RP + RT	Single, NA	No	Wedge resection	Biochemical response at 47 months
	T3aN0	4 + 4	RP + RT	Single, NA	No	Wedge resection	Biochemical response at 23 months
	T2cN0	4 + 3	RP + RT	Single, NA	No	Wedge resection	Biochemical response at 17 months

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Table 1 Continued

Author	TN Stage	Gleason Score	Initial Management	Metastases	ADT	Metastatic Management	Follow-up
	T2bN0	3 + 4	RP	Two, NA	No	Wedge resection	Biochemical response at 77 months
	T3aN0	4 + 4	RP + RT	Six, NA	No	Wedge resection	Biochemical response at 26 months
	T3aN0	4 + 4	RP + RT	Two, NA	No	Wedge resection	Biochemical response at 12 months
Present case report	T1bN0	5 + 3	Adenectomy + RT	Two, max 1.5 cm	Bicalutamide + LHRH agonist	Lobectomy	Biochemical response at 32 months

PubMed and Google Scholar research, performed September 30, 2019: ("lung" [MeSH Terms] OR "lung" [All Fields] OR "pulmonary" [All Fields]) AND ("neoplasm metastasis" [MeSH Terms] OR "neoplasm" [All Fields] AND "metastasis" [All Fields]) OR "neoplasm metastasis" [All Fields] OR "metastasis" [All Fields] AND ("prostate" [MeSH Terms] OR "prostate" [All Fields]) AND ("neoplasms" [MeSH Terms] OR "neoplasms" [All Fields] OR "cancer" [All Fields]).

Abbreviations: ADT = androgen deprivation therapy; GnRH = gonadotropin-releasing hormone; LHRH = luteinizing hormone-releasing hormone; mPC = metastatic prostate cancer; NA = not assessed; PC = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; TURP = transurethral resection of the prostate.

agonist. However, not even that addition was able to stop PSA growth, which continued to progress up to 0.78 ng/mL, with a castration level of serum testosterone (below 0.2 ng/dL).

In October 2016, a multidisciplinary discussion among the oncologist, urologist, and thorax surgeon led them to share the option of a lung lower lobectomy. As the patient agreed, he underwent a lower lobectomy in November 2016. Immune histochemical analysis confirmed metastases from prostatic adenocarcinoma, with diffuse and intense nuclear positivity for androgen receptors, PSA absence, and isolated cells that were chromogranin-A positive in a small area of lung metastasis, compatible with a neuroendocrine differentiation (Figure 2). After lobectomy, PSA became undetectable, and ADT was stopped.

In July 2019, 32 months after the lobectomy, his PSA was stable at 0.07 ng/mL, his Eastern Cooperative Oncology Group performance status was 0, and he is continuing surveillance in absence of ADT.

## Discussion

The oligometastatic state is an intermediate stage of cancer spread between localized disease and widespread metastases.<sup>9</sup> This condition represents a therapeutic "gray zone" for many different tumors as well as PC. To date, according to the major international guidelines,<sup>7,8</sup> ADT is the gold standard in the management of such patients, whereas the impact of local tumor ablative therapy in oligometastatic PC is still under debate. However, over the last few years, metastasis-directed therapy has also been gaining importance for patients with PC, with stereotactic body radiotherapy representing the most experienced treatment option.<sup>10</sup> Literature data concerning lung metastasectomy in patients with oligometastatic PC is limited, with less than 20 single cases and a unique case series of 9 patients from a single institution published (Table 1).

The typical patient who develops such pulmonary metastases, as can be guessed, is a patient with an elevated Gleason score, previously subjected to radical prostatectomy sometimes followed by salvage radiotherapy. In the literature, 18 (66.7%) of 27 patients presented a single pulmonary metastasis, whereas in other cases, the

nodes were multiple. In 12 (44.4%) of 27 patients a surgical resection of metastases was associated with an ADT.

Taking into account the huge limits of the heterogeneity of the PC, the patients, the type and number of pulmonary metastases, the adjuvant ADT, and the different follow-up, the previous reports show that 88% of the patients presented a good response to surgical therapy.

In most of the reports, this success was evaluated with a biochemical response or with no further metastasis on subsequent imaging.

All 3 patients who did not benefit from surgery were patients who underwent ADT following surgery. However, this could be influenced by the limited number of the sample as well as publication bias.

The data on patients' symptoms or quality of life was not presented in most reports.

We believe that our case may be emblematic. This is a patient with PC who has undergone surgery and radiotherapy for PC. He became metastatic about 8 years after RT and was treated with LHRH agonist and anti-androgens until the development of castration resistance. He underwent surgical resection of lung metastasis, and the ADT was stopped. The histologic examination showed cells with neuroendocrine immunohistochemical phenotype. Thirty-two months after the lobectomy, his PSA was stable at 0.07 ng/mL, his Eastern Cooperative Oncology Group performance status was 0, and he is continuing active surveillance in the absence of ADT.

Nowadays, the indication and role of surgical resection of metastasis in patients with PC is not as defined as in other oncologic diseases, where metastasis resection in patients with oligometastatic disease is recommended in national and international guidelines.<sup>4</sup>

Although with significant limitations, the reports currently available in the literature show that a surgical approach to lung lesions can be beneficial in terms of biochemical response and disease-free survival.

Furthermore, in patients eligible for this surgery, resection of the metastases could be useful for patients who are not responsive to ADT, while also avoiding side effects.

Indication for a surgical resection should be limited to selected cases after multidisciplinary team discussion.

Although prospective studies on larger series are needed, the surgical resection of PC lung metastasis seems to be feasible, effective, and safe in appropriate patients.

## Disclosure

The authors have stated that they have no conflicts of interest.

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