

Review

Metachronous Single Pulmonary Metastasis of Prostate Cancer: Report of a Rare Case and Literature Review

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Abstract. *Background:* Prostate cancer recurrence after definitive local therapy usually involves the bone and regional lymph nodes. *Case Report:* We present the case of a 72-year-old male patient with an isolated lung nodule, seven years after radical prostatectomy for prostate cancer, pT2bN0 and Gleason score 7(4+3), and prostatic-specific antigen (PSA) levels within normal limits. The nodule was considered as a primary lung cancer and the patient was subjected to lobectomy. The immunohistochemical staining showed that the tumor was PSA(+) and NKX3.1 (+), revealing that it was metastasis from prostatic cancer and that wedge resection was the proper procedure. Three years later the patient is disease-free, suggesting the importance of aggressive treatment of oligometastatic disease. *Conclusion:* Metastasis to the lung is present in more than 40% of men with metastatic prostate cancer; however, lung metastases without any bone or lymph node involvement are extremely rare and only a handful of cases are reported in the literature. Surgical excision of the metastatic lung site is the most common therapeutic approach associated with a good prognosis.

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Prostate cancer is one of the most common cancers affecting males worldwide, with a generally favorable prognosis (1). Metastatic prostate cancer recurrence after definitive local therapy can occur in any tissue with bone and regional lymph nodes being the most common metastatic sites (2). Metastasis to the lung is present in more than 40% of men with metastatic prostate cancer (3); however, lung metastases without any bone or lymph node involvement and low Gleason score are extremely rare and only a handful of cases are reported in the literature (4).

Herein, we report a case of a 72-year-old male with a solitary pulmonary metastasis from prostate cancer with a disease-free interval of 7 years and no extrapulmonary metastases. In addition, we provide a review of the current literature.

Case Report

A 72-year-old, Caucasian, ex-smoker male patient underwent radical prostatectomy with bilateral lymphadenectomy in 2011. Pathological examination of the resection specimen revealed a Gleason 7 (4+3) prostate adenocarcinoma, pT2bNo without perineural and vascular invasion, extra-capsular extension, and negative surgical margins. The pre- and post-operative prostate specific antigen (PSA) level was 4.3 ng/ml and undetectable, respectively, and the patient did not receive any adjuvant treatment such as external beam radiotherapy (EBRT) or adjuvant hormonal-therapy (HT). The patient underwent a close biannual follow up and remained disease-free.

Approximately, 7 years after the primary surgery, due to an increase in PSA levels (0.9 ng/ml), a bone scan and an abdominal, pelvic, and lung computed tomography (CT) scan was performed, revealing only a solitary lung nodule with a maximum diameter of 3.3 cm, located in the right lower lobe without any other pathological findings (Figure 1). Then, a positron emission tomography (PET) was performed without

Table I. Review of the current literature.

Authors (Year) (Ref)	Number of cases	Age	PC characteristics	PC treatment	Time to relapse	Site of relapse	PSA at relapse	Lung metastasis treatment	Outcome
Varkarakis <i>et al.</i> , 1974 (5)	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rockey <i>et al.</i> , 1990 (6)	1	83	Low-grade adenocarcinoma	RT	8 y	Left lower lobe	3.7 ng/ml	Orchiectomy	N/A
Fabozzi <i>et al.</i> , 1995 (7)	11	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Smith <i>et al.</i> , 1999 (8)	1	70	PT2 GS: 4+5	Radical prostatectomy	2 y	Right lower lung	2.1 ng/ml	Lobectomy	N/A
Hofland <i>et al.</i> , 2000 (9)	1	49	T3cNoMo GS: 4+5	Radical prostatectomy	4 y	Left lower lobe	1 ng/ml	Lobectomy	Brain relapse
Chao <i>et al.</i> , 2004 (10)	1	68	T2a GS:4+5	Radical prostatectomy	15 m	Left lower lobe	0.4 ng/ml	Wedge resection	At least 12 y DFS
Pruthi <i>et al.</i> , 2007 (11)	1	72	T2bN0 GS: 3+3	Radical prostatectomy	4 y	Right lower lobe	2.3 ng/ml	Endocrine therapy	Lung relapse after 2y
Khandani <i>et al.</i> , 2009 (12)	1	78	UD	RT	15 y	Left lower lobe	8.5 ng/ml	Surgical resection and mediastinal LND	N/A
Boyer <i>et al.</i> , 2009 (13)	1	65	pT2 GS: 3+3	Radical prostatectomy	11 y	Left upper lobe	10.56 ng/ml	Surgery	At least 11 y DFS
Goto <i>et al.</i> , 2010 (14)	1	73	pT4 GS: 4+5 adenocarcinoma+undifferentiated sarcomatoid carcinoma	Neoadjuvant Endocrine therapy+ pelvic evisceration	3 m	Right lung	WNL	Wedge resection +CHEMO	At least 10 m DFS
Pepe <i>et al.</i> , 2012 (15)	1	75	pT3aNO GS: 4+3	Radical prostatectomy	9 y	Left upper lobe	Undetectable	Segmental resection	At least 6 m DFS
Calais <i>et al.</i> , 2014 (16)	1	67	T1cN0M0 GS: 4+4	RT+Endocrine therapy	7 y	Right middle lobe	4 ng/ml	Lobectomy	N/A
Maebayashi <i>et al.</i> , 2015 (17)	1	50	cT4N0M0 GS: 4+5	Endocrine therapy+RT	1 y	Left lung	WNL	Lobectomy and mediastinal LND+chemo +RT	30 m OS
Gago <i>et al.</i> , 2016 (18)	1	62	pT3a pNx GS: 7	Radical prostatectomy	7 y	N/A	N/A	N/A	N/A
Mortier <i>et al.</i> , 2017 (19)	1	82	pT3a GS: 6	Radical prostatectomy+RT +Endocrine therapy	9 y	Right lower lobe	3.32 ng/ml	Lobectomy	At least 1 y DFS
Iijima <i>et al.</i> , 2017 (20)	1	71	N/A	Radical prostatectomy	12 y	Right upper lobe	WNL	Lobectomy and mediastinal LND	At least 2y DFS
Rush <i>et al.</i> , 2017 (21)	1	70	T4N0M0 GS: 4+4	Radical prostatectomy+RT	10 m	Right lung	2.9 ng/ml	Segmentectomy	At least 2y DFS
Große Hokamp <i>et al.</i> , 2017 (22)	1	63	N/A	Radical prostatectomy+RT +endocrine therapy	4 y	Right lung	1.60 ng/ml	Resection	N/A
Boschian <i>et al.</i> , 2018 (23)	1	69	pT3aN0M0, GS: 4+3	Radical prostatectomy+RT	3 y	Left lower lobe	0.4 ng/ml	Segmental resection with LND	At least 3y DFS
Polverari <i>et al.</i> , 2019 (24)	1	78	pT2cN0 GS: 4+3	Radical prostatectomy	14 y	Right upper lobe	0.33 ng/ml	Wedge resection and mediastinal LND	N/A
Yoshitake <i>et al.</i> , 2021 (25)	1	83	GS: 5	RT	8 y	Right middle lobe	WNL	Lobectomy and hilar and mediastinal LND	N/A

Table I. Continued

Table I. *Continued*

Authors (Year) (Ref)	Number of cases	Age	PC characteristics	PC treatment	Time to relapse	Site of relapse	PSA at relapse	Lung metastasis treatment	Outcome
Maru <i>et al.</i> , 2021 (4)	1	77	T2bN0 GS: 3+4	Prostatectomy	14 y	Left upper lobe	0.412 ng/ml	Left upper lobectomy with hilar and mediastinal LND	At least 16m DFS
Muro <i>et al.</i> , 2015 (26)	1	79	cT3aN0M0 GS: 4+3	RT+combined androgen blockade	3 y	Right lower lobe	0.03 ng/ml	Wedge resection +endocrine therapy	At least 18 m DFS
Zograbyan <i>et al.</i> , 2021 (27)	1	78	T1cN0M0 GS: 8	RT+endocrine therapy	7 y	Right upper lobe	N/A	N/A	At least 5 y OS
Current	1	72	T2bN0M0 GS: 4+4	Radical prostatectomy	7 y	Right lower lobe	0.9 ng/ml	Lobectomy with hilar and mediastinal LND	At least 3 y DFS
Wu <i>et al.</i> , 2020 (28)	1	74	cT4 GS:4+4	Endocrine therapy	Concurrent	Right lower lung	3 ng/ml	Radical resection of the right upper lung	At least 3 y PFS
Kosaka <i>et al.</i> , 2022 (29)	1	61	cT3a GS: 7	Laparoscopic-assisted radical prostatectomy	16 m	Left lower lobe	0.40 ng/ml	Thorascopic wedge resection	At least 3 y DFS

LND: Lymph node dissection; PC: prostate cancer; DFS: disease-free survival; GS: Gleason score; N/A: not available; RT: radiotherapy; Time to relapse: time between radical PC treatment and lung metastases; PSA: prostate-specific antigen; WNL: within normal limits; y: years; m: months.

revealing any abnormal accumulation in other organs, apart from the lung nodule (18.4 SUV), strongly suggesting a primary lung cancer (cT2aN0M0), with no elevation in any other serum tumor biomarkers (carcinoembryonic antigen, carbohydrate antigen 19.9, squamous cell carcinoma antigen, neuron-specific enolase).

The patient underwent a thorascopic radical resection of the right lower lobe with hilar and mediastinal lymph node dissection as a radical surgery for primary lung cancer under general anesthesia, with the histological examination revealing an adenocarcinoma, with negative lymph nodes. Immunohistochemical staining showed TTF1 (-), p63(-), napsin A(-), PSA(+), CK7(+), and CK20(+) regionally (EIKONA) and the histopathological review comparing this tissue and the one from the prostatectomy confirmed the diagnosis of low differentiated adenocarcinoma metastatic from prostate cancer, with both tumors also positive for NKX3.1 (+).

Based on these results the patient received salvage radiotherapy (RT) to the prostatic bed and received six months of androgen deprivation therapy (ADT). Three years later he remains disease-free.

Literature Review

An extensive systematic literature search of the scholar databases Medline, Web of Science, and Scopus resulted in the retrieval of 26 articles reporting cases of prostate cancer with a single lung metastasis (4-29). In total, 35 cases

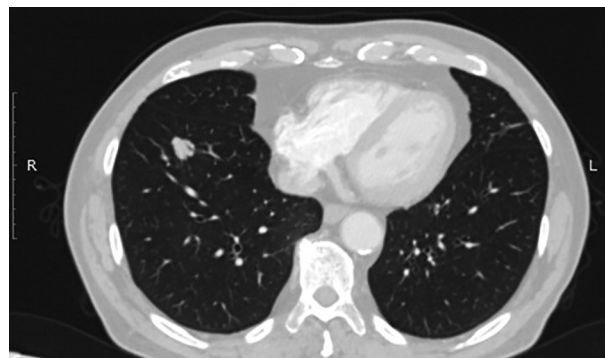


Figure 1. Computed tomography revealing the metastatic site located in the right lower lung.

(including the present one) were found, with the first case being reported in 1974. The time interval between the prostate cancer and lung metastasis varied, ranging from concurrent diagnosis (28) to 15 years after the first diagnosis (12), with a mean recurrence time of 68.2 months.

Table I displays the data regarding the time and site of recurrence, the therapeutic approach that followed for both the primary prostate cancer and the lung metastasis and PSA levels measured at the time of diagnosis of the metastasis. Secondary disease was located similarly in both lungs, with 14 cases located in the right lung and 11 in the left one. Furthermore, in the majority of cases, the metastatic site was treated surgically, with only two cases treated with

hormonotherapy and orchiectomy (6, 11). Most of the cases had good prognosis with more than 6 and 12 months disease-free survival (Table I).

Discussion

It is well known that prostate cancer has a high prevalence of osteoblastic bone and lymph node metastasis (2). It, however, seems highly feasible for prostate cancer to hematogenously spread to the lungs as it does to the bones. Lung-only metastasis, however, comprises less than 1% of all metastatic prostate cancers (2), as presented at Table I.

Elevation of the PSA levels generally precedes the radiologic findings of local or distant recurrence. Therefore, increased serum PSA levels without detectable cancer recurrence is expressed as a biochemical recurrence (30). In this case, in our attempt to identify whether this was a biochemical, local, or metastatic recurrence we identified a solitary lung nodule. Due to the rarity of solitary lung metastasis from prostate cancer, especially with low Gleason score, patient history of smoking, low levels of PSA (0.9 ng/ml) and because any biopsy of the nodule was considered too risky, a lobectomy was conducted believing that this was a second primary cancer.

Perhaps, if ^{68}Ga -PSMA ligand PET/CT imaging was available, it would confirm prostate cancer recurrence, since it has higher detection rates than other imaging methods, even with PSA <0.5 ng/ml (31). In this case, a wedge resection could have been performed, which is the standard procedure for metastatic prostate cancer to the lung aiming at the preservation of lung parenchyma, since there are exploratory results suggesting that metastasectomy and radiotherapy with curative intent are promising approaches for oligometastatic prostate cancer (32-35). In fact, pulmonary metastatic lesions that underwent metastasectomies have been closely related to survival advantages in various cancers, including colon cancer and uterine cervical cancer (36, 37). Oligometastases have been described in different types of tumors, can be considered as an intermediate state between non metastatic and widespread metastatic disease (38) and is a challenging and unique situation. Although no consensus definition for oligometastatic disease exists, most clinical trials have used either three or five metastatic sites on conventional imaging to define oligometastatic prostate cancer (33).

It is obvious from Table I that surgical resection was the preferred treatment in most cases, for 10 patients it was lobectomy, and for 8 patients it was wedge resection, with satisfactory results in most cases. In two cases, the patients were reported to be disease-free for more than ten years after the surgery. Most patients had a long survival between the radical prostate cancer treatment and the detection of metastasis. As far as the PSA level is concerned, it is

interesting that most patients had a biochemical recurrence, but the PSA level was within normal limits (median PSA=2.1 ng/ml), which may be explained by the low disease burden. This probably suggests that perhaps many lung metastases have been misdiagnosed as primary lung cancers, therefore, thorough investigation should be performed, including ^{68}Ga -PSMA ligand PET/CT imaging and a histopathological review.

Conclusion

Prostate cancer can surprise clinicians by its various manifestations. Metastatic disease exclusive to the lung in prostate cancer is extremely infrequent. This case demonstrates that thorough investigation should be performed before every therapeutic decision and that aggressive treatment of oligometastatic disease may be optimal in the management of these patients.

Conflicts of Interest

The Authors declare no potential conflicts of interest in relation to this study.

Authors' Contributions

Study conception and design: Kokkalis A., Tsapakidis K.; Acquisition of data: Kokkalis A., Samara A, Papadopoulos V, Tolia M.; Analysis and interpretation of data: Papadopoulos V., Tolia M., Tsoukalas N.; Drafting of manuscript: Kokkalis A., Samara A.; Critical revision: Tsapakidis K., Papadopoulos V., Tolia M., Tsoukalas N.

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