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# Prostate Cancer Patient With Lymph-node Metastasis Treated Only With Methionine Restriction Has Stable Disease for Two Years Demonstrated With PET/CT and PSMA-PET Scanning and PSA Testing

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**Abstract.** *Background/Aim: Metastatic prostate cancer is a recalcitrant disease. Our laboratory has previously treated prostate-cancer patients with methionine restriction effected by a low-methionine diet and oral recombinant methioninase (o-rMETase), both alone and in combination with other agents. The present case is a 66-year-old patient who had a radical prostatectomy in 2019 with a Gleason score 3+3 and 3+4. The patient subsequently was treated with immunotherapy in 2021 and salvage proton-beam therapy in 2022, and then treated only with o-rMETase and a low-methionine diet. The aim of the present study was to determine the long-term efficacy of methionine restriction on the patient's prostate cancer. Case Report: Starting in September 2022, the patient started methionine restriction with a low-methionine diet and o-rMETase, twice a day, after meals, at 250 units/dose. Since the start of methionine restriction, the patients' prostate-specific antigen (PSA) has remained stable, under 2 ng/ml. Positron emission tomography/computed tomography (PET/CT) and prostate specific membrane antigen (PSMA)-PET imaging indicated in September 2023 a right pelvic-side-wall metastatic lymph node that was stable when the PSMA-PET scan was repeated in March 2024, with the standardized uptake value (SUV) decreasing from 19.39 to 14.98. A very small possible metastatic external-iliac lymph node was detected in March 2024. Thus, the lymph-node metastases were stable and did not increase. Conclusion: During the time the patient was on methionine restriction alone, effected by a low-methionine diet and o-rMETase, the metastatic prostate cancer did not progress. Further clinical studies of methionine restriction and metastatic prostate cancer are needed, including randomized clinical trials.*

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Metastatic prostate cancer is a recalcitrant disease treated by androgen-deprivation therapy (ADT) (1) and chemotherapy if the patient becomes resistant to ADT (2).

Our laboratory has discovered that methionine addiction, termed the Hoffman effect, is a fundamental and general hall-mark of cancer (3, 4). We have shown that methionine addiction of cancer is effectively treated by methionine restriction with oral recombinant methioninase (o-rMETase) in mouse models of all major tumor types, including patient-derived orthotopic xenograft (PDOX) models (5-23).

Patients with prostate cancer have been treated with methionine restriction comprising o-rMETase, a low-methionine diet alone or in combination with chemotherapy, with promising results (24-26).

Previously a 76-year-old male with bone-metastatic prostate cancer, took o-rMETase twice a day at 250 units per dose for three months, during which the patient's prostate-specific antigen (PSA) dropped approximately 70%. During this time the patient's hemoglobin increased (24). In another previous case, a patient had a rapid rise in PSA levels, from 39 to 56

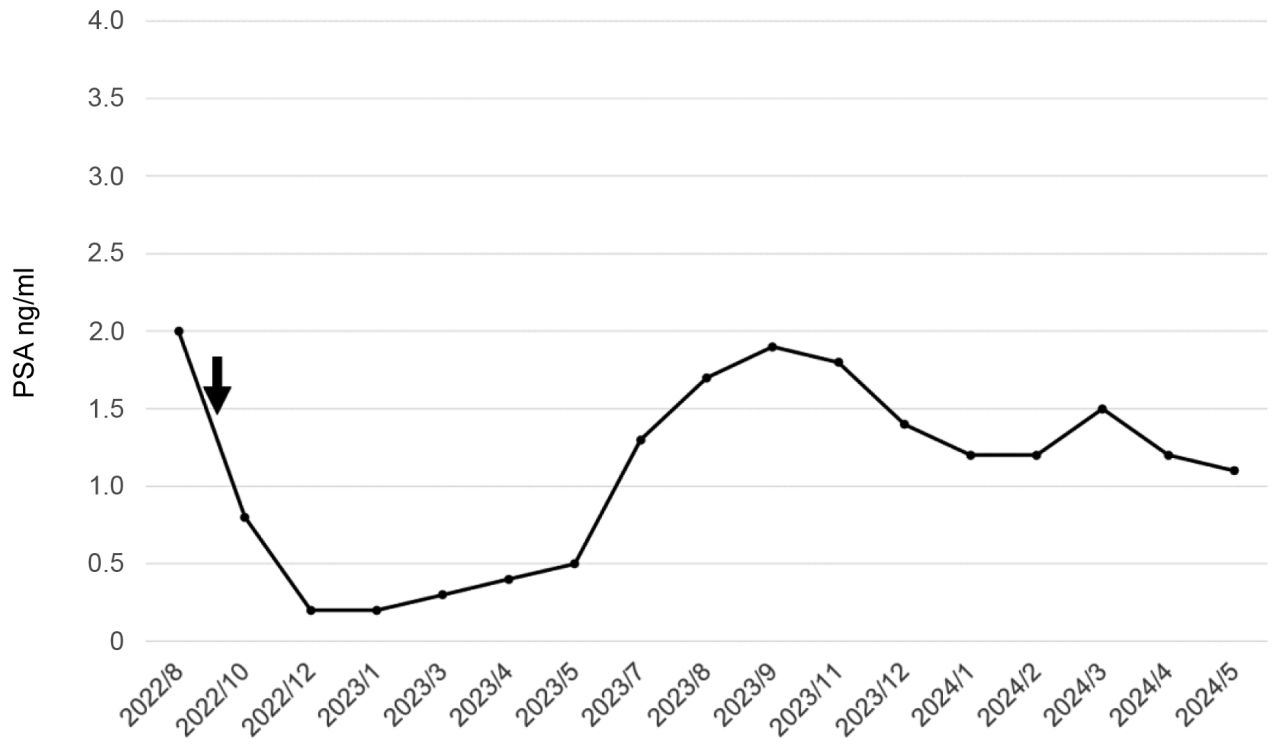


Figure 1. *Time course of changes in prostate-specific antigen (PSA) levels (ng/ml) in a patient with metastatic prostate cancer treated with oral methioninase (o-rMETase) and a low methionine diet. The solid arrow indicates the start of o-rMETase and low-methionine diet (2022/9).*

ng/ml, within 6 weeks. At the 15th week of o-rMETase administration, the PSA levels stabilized at 62 ng/ml. No overt side effects were observed (25). In another previous study, two advanced prostate-cancer patients took o-rMETase for approximately one month. One of the patients taking o-rMETase showed a 38% reduction of PSA levels and the second patient showed a 20% PSA reduction (26).

The present study is on a metastatic prostate-cancer patient who for the last two years was only treated with methionine restriction including o-rMETase and a low-methionine diet and has had a stable PSA and no further growth of a lymph node metastasis.

## Case Report

The present case is a 66-year-old male who had a radical prostatectomy in 2019 with Gleason score 3+3 and 3+4. The patient subsequently was treated with immunotherapy in 2021 and salvage proton-beam therapy in 2022. Starting in September 2022, the patient started methionine restriction with a low-methionine diet and o-rMETase, twice a day after meals at 250 units/dose. Since the start of methionine restriction, the patients' PSA has remained stable under 2 ng/ml (Figure 1). Positron emission tomography/computed tomography (PET/CT) and prostate specific membrane antigen (PSMA)-PET imaging indicated in September 2023 a right pelvic side wall metastatic lymph node that was stable when the PSMA-PET scan was repeated in March 2024, with the standardized uptake value (SUV) decreasing from 19.39 to 14.98. A very small possible metastatic external-iliac lymph node was detected in March 2024. Thus, the lymph-node metastases were stable and did not increase during methionine restriction.

## Discussion

The present patient had been previously treated with a radical prostatectomy, immunotherapy and with proton beam radiation therapy. Since September 2022, the patient has only been on methionine restriction effected by a low-methionine diet and o-rMETase. The patient's PSA has remained under 2 ng/ml for this time period (Figure 1) and a metastatic lymph node has not grown, as detected with PSMA scans, which are very sensitive. Previously we have treated prostate-cancer patients with o-rMETase and in one case observed a 70% reduction in PSA over 3 months (24) and in other cases decreasing PSA, as well as stable disease (25, 26).

The present case shows promise for prostate-cancer patients to be treated with methionine restriction. Additional studies are needed, including randomized clinical trials, to demonstrate the efficacy of rMETase on prostate cancer.

Methionine restriction is effective because it targets the fundamental hallmark of cancer (3, 4, 27-50).

o-rMETase is showing clinical promise in other cancer types in addition to prostate cancer (28, 51-57).

## Conflicts of Interest

The Authors declare no competing interests.

## Authors' Contributions

SM was a major contributor to writing the manuscript and RMH revised the paper. QH produced o-rMETase and critically read the manuscript. KM, BMK, MS, MB, NY, KH, HK, SM, KI, TH, HT and SD critically read and approved the final manuscript.

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